The neurobiological basis of treatment response in psychosis

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Abstract

Antipsychotic treatment response is unpredictable and variable, and there are currently no reliable neurobiological assessment methods to predict treatment efficacy. Previous research suggests that psychosis is associated with several brain abnormalities and that some of these may be associated with poorer treatment response.

This thesis investigated the association between brain function (salience attribution during fMRI and perfusion) and treatment response at 4 and 12 weeks in antipsychotic-naïve patients with their first episode of psychosis. Twenty-five first episode psychosis patients took part in a longitudinal, open-label intervention study, undergoing neuroimaging at baseline and again after treatment with an antipsychotic medication. Matched healthy controls were recruited and underwent two scans across a similar period. Treatment response in patients was assessed using the Positive and Negative Syndrome Scale. Seventeen patients were classed as responders and eight were non-responders. These groups were compared with each other and with healthy controls to explore differences in neurobiological measures associated with treatment response.

A good response was associated with higher implicit adaptive salience scores at baseline. Successful treatment also appeared to be associated with significant decreases in implicit aberrant salience, which was seen in responders but not non-responders. There were also differences in neural activation patterns of responders and non-responders, with greater adaptive salience activation in the insula and midbrain in four-week responders than in non-responders before and after treatment, respectively. Responders and non-responders also differed in terms of resting cerebral blood flow (rCBF), with responders showing higher cerebellar and thalamic rCBF at baseline compared with non-responders. Furthermore, higher baseline thalamic rCBF was positively correlated with lower

positive PANSS scores at follow up, suggesting an association between thalamic perfusion and response. Neurobiological differences between responders and non-responders were more marked than those between patients and controls.

Heterogeneity in terms of response to treatment may reflect differences in the underlying neurobiology. Such results may inform personalised treatment of psychosis, allowing antipsychotic medication to be selected based on neurobiology rather than through trial and error.

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List of abbreviations

5HT Serotonin

BPRS Brief Psychiatric Rating Scale

cASL Continuous Arterial Spin Labelling

CBF Cerebral Blood Flow

CBV Cerebral Blood Volume

CGI Clinical Global Impression

$CMRO_2$ Blood Oxygenation

CS Conditioned Stimulus

DSM-IV Diagnostic and Statistical Manual of Mental Disorders IV edition

DUP Duration of Untreated Psychosis

FEP First Episode Psychosis

FGA First Generation Antipsychotic

fMRI Functional Magnetic Resonance Imaging

GM Grey Matter

ICD International Classification of Diseases

MID Monetary Incentive Delay

MRS Magnetic Resonance Spectroscopy

NICE National Institute for Health and Care Excellence

OPTIMISE Optimization of Treatment and Management of Schizophrenia in Europe

PANSS Positive and Negative Syndrome Scale

PET Positron Emission Tomography

PFC Prefrontal Cortex

SANS Scale for the Assessment of Negative Symptoms

SAPS Scale for the Assessment of Positive Symptoms

SAT Salience Attribution Task

SGA Second Generation Antipsychotic

SLAM South London and Maudsley

SMI Severe Mental Illness

SVM Support Vector Machine Learning

UHR Ultra High Risk

VTA Ventral Tegmental Area

WHO World Health Organisation

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Personal Contributions

The data forming this PhD project was collected as part of the phase four clinical trial, 'Optimization of Treatment and Management of Schizophrenia in Europe' (OPTiMiSE). I joined the OPTiMiSE KCL study team in 2011, and I have participated in recruitment, clinical assessment, MRI scanning, and data analysis as follows:

Recruitment: From 2011 to 2015, I recruited patients from across South London and the Maudsley (SLAM) NHS Trust, in particular attending clinic referral meetings at Lambeth Early Intervention service (LEO), as well as by contacting services by phone and/or email each week. I identified and screened eligible participants using ePJS and in liaison with their clinical team. I presented the study to potential participants and took additional consent for the MRI components investigated in this thesis (consent for the clinical trial had to be obtained by a psychiatrist). In addition, I recruited, screened, and consented matched healthy controls.

Clinical assessment: I rated psychotic symptoms using the PANSS, and completed the full battery of clinical assessments required for OPTiMiSE. I converted all PANSS scores into PPHS ratings, and was solely responsible for collating and analysing the clinical data in this thesis.

Other assessments: I developed the healthy control protocol, ensuring that baseline and follow up data were obtained in the control group. I completed assessments for healthy controls, including measures of depression and anxiety, demographics, medical and drug histories, and cognitive assessments.

MRI: I have been responsible for organizing and coordinating the scanning arm of the study. I booked scan slots, screened patients for safety and eligibility for MRI, coordinated transport of participants to and from the scan, and attended all

baseline and follow up scanning sessions. At these sessions, I trained participants for the SAT, and implemented the task during scanning.

I was the sole researcher analyzing the cASL and fMRI data, as well as the SAT behavioural data. I conducted the analyses investigating the relationships between these measures and treatment response, under the guidance of my PhD supervisors.

1. INTRODUCTION

1.1. Schizophrenia

1.1.1. Early conceptualisations

The nonspecific concept of “madness” as wild, chaotic or bizarre behaviour has been a part of human culture for many hundreds, if not thousands, of years. With the birth of psychiatry in the 1800s as a medical discipline, disordered individuals were mainly confined in asylums or hospitals. There were few treatments and few categorisations of different subtypes of mental illness. Over the past century, classification of mental illness has yielded a range of disorders outlined in diagnostic manuals, such as the International Statistical Classification of Diseases and Health Problems (ICD-10; World Health Organisation, 2011) and the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013). Many mental illnesses are now recognised to be commonly occurring and representing a major contribution to the global burden of disease (Kessler et al. 2009).

Early attempts to subdivide 'insanity' into different disorders began in the 19th century. The current conception of schizophrenia was developed from early observational work of Emil Kraepelin in the 1800s. At this time, Kraepelin laid out an early classification of mental disorders in the 6th edition of *Psychiatrie* (Kraepelin, 1899), identifying what he called ‘dementia praecox’ in a number of his patients. This was differentiated from manic-depressive illness (encompassing a range of current mood disorders including bipolar and major depression) and Kraepelin emphasized the cognitive impairments he observed, highlighting the presence of a progressive deterioration over time in such patients. Interestingly, Kraepelin saw dementia praecox as primarily the outcome of brain disease, a theory that was fiercely contested in the following decades. However, the concept of schizophrenia as a disorder with a biological basis seated in the brain has endured.

Later psychiatrists have focused less on the cognitive symptoms and turned instead to the positive symptoms (experiences that are present when normally they would not be) and negative symptoms (experiences that represent a loss or impairment of normal function or experience). In the early 20th century, Eugen Bleuler revised and expanded on Kraepelin's concept of dementia praecox, and coined the term 'schizophrenia' and believed that dementia, or progressive deterioration, was not inevitable. He emphasized a splitting of psychic functioning (the "split mind" of this term) as a core symptom, via which the unity of the personality is lost. Primary symptoms were seen to be blunted affect, loosening of associations, ambivalence, and autism. Delusions and hallucinations were seen as secondary. In the 1950s, Kurt Schneider also proposed a hierarchy of symptoms, with a greater emphasis on delusions and hallucinations. The importance of positive symptoms in the diagnosis of schizophrenia still dominates today, although more recently cognitive impairments have again begun to assume importance and attention (Keefe, 2008).

Conceptualising mental disorders as discrete illness categories, with commonly occurring signs and symptoms that differentiate them from other psychiatric illnesses, allows for the development of specific treatment and care management strategies. Diagnostic categories indicate specific psychological and pharmacological treatments, and guide research into new treatments. However, recent research takes account of the complexity and heterogeneity *within* diagnostic categories. As I shall lay out in this thesis, research is beginning to move even further beyond treatments targeted at groups of individuals with a shared diagnosis towards personalised treatment, in which individual underlying neurobiological and physiological dysfunctions are specifically targeted.

1.1.2. Diagnosis, prevalence and prognosis

Schizophrenia is a severe mental illness (SMI) affecting just under 1% of the population worldwide. It is found in all cultures and geographical regions, and is recognised as a

major cause of chronic disability in adults (Perala et al., 2007). Onset is usually in adolescence and early adulthood, but is preceded by a period of prodromal subclinical symptomatology. Schizophrenia encompasses a range of symptoms not attributable to organic pathology, reactions to drugs or severe anxiety. Symptoms can be divided into positive psychotic symptoms (delusions, hallucinations, and formal thought disorder) and negative symptoms (avolition, apathy, asociality, flattened affect, anhedonia, and poverty of thought/speech), alongside neurocognitive deficits. Diagnosis is made clinically using operationally defined criteria outlined in the ICD-10 and DSM-IV, and there are presently no diagnostic tests available. Psychotic symptoms may however be present in several other psychiatric disorders; these are differentiated by several factors, including associated substance use, and whether depression or mania are present (Van Os and Kapur, 2009).

This thesis focuses solely on psychotic symptoms within the context of schizophrenia (including the diagnoses of schizoaffective and schizophreniform disorders). Still, it should be considered that there is considerable heterogeneity of clinical presentations even within schizophrenia. Furthermore, prognosis and long-term outcomes of schizophrenia are also heterogeneous, with many factors influencing outcome, including duration of untreated psychosis (DUP) and socio-environmental factors. This makes it difficult to predict the course, outcome of treatment, and long-term prognosis of an individual presenting with psychotic symptoms. Although outcome is variable, in contrast to accepted pessimism regarding prognosis in psychosis, symptomatic remission and recovery are more common than previously suggested (Revier et al., 2015). However, social recovery appears to be much less common, with fewer improvements seen in terms of work and relationships. It is increasingly acknowledged that experiencing psychosis does not necessarily indicate that an individual will go on to experience chronic schizophrenia. Whilst some patients may remain continuously ill or experience further episodes of illness between periods of relative health, others experience full recovery after a single episode (Revier et al., 2015).

Outcomes, including long-term prognosis and response to antipsychotic treatment are variable and unpredictable. Understanding the pathophysiology underlying schizophrenia may be helpful in discovering prognostic biomarkers to improve prediction of outcomes. This thesis aims to improve understanding of the heterogeneity in response to antipsychotic treatment in a sample of first episode psychosis patients. Improving prognostic prediction amongst such patients will inform care and management of their disorder, potentially allowing greater personalisation of treatment and improving outcomes. SMI, such as schizophrenia, have both short- and long-term adverse effects on behaviour and function, which are not only damaging to the individual and their families, but also represent a significant cost to society (Mangalore and Knapp, 2007). Therefore, research to improve the treatment and management of the disorder has clear benefits to public health, as well as on a personal level to relieve the suffering of those with the disorder.

1.1.3. Risk factors

Despite advances in our understanding of schizophrenia, the precise cause of the disorder is still unclear, with potential psychosocial, genetic, and biological mechanisms of aetiology posited. Generally, a more holistic biopsychosocial model has been developed, acknowledging the interplay between these different factors. In particular, interactions between genes and the environment have been investigated, although challenges remain in elucidating the role of such interactions in the disease aetiology (Van Os et al. 2008).

Obstetric factors, including complications during pregnancy and birth, have been implicated in vulnerability for schizophrenia (Cannon et al., 2002), potentially increasing the risk of disrupted neurodevelopment. Neurodevelopmental models of schizophrenia propose that normal brain development is disrupted in utero with subsequent disruptions during critical stages of early childhood and adolescence (Murray et al., 2008; Owen et al., 2011). Consistent with this, neurological soft signs (that indicate

non-specific cerebral dysfunction) are seen in excess in schizophrenia (Dazzan et al., 2008), and may indicate a more severe, chronic illness course (Varambally et al., 2012). Further, several brain morphological abnormalities, present before illness onset, have been associated with schizophrenia, including ventricular enlargement, reduced cortical folding, and lack of normal brain asymmetry, and these may result from neurodevelopmental insults (Pantelis et al., 2005). Unfortunately, antipsychotic medication complicates the interpretation of brain changes, as observed neurobiological alterations could result from the effects of antipsychotics rather than being primary to the disease process (see chapter 1.5).

Genetics represent a further risk factor for schizophrenia. Relatives of those with the disorder are at an increased risk of developing the disorder compared with the general population. Moreover, first-degree relatives are at greater risk than second-degree relatives (Ban, 2004). Twin studies also support a role for genes, with higher concordance rates between monozygotic twins than between dizygotic twins (Kringlen, 2000). These results, alongside heritability estimates of around 80%, suggest a strong genetic component to the disorder, yet no one causative gene has been implicated. Rather, genetic studies support complex interactions amongst multiple genes (Owen et al., 2005). Indeed, genome wide association studies (GWAS) have, in some cases, identified over 100 genes that appear to confer risk for schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Many genes identified by GWAS are biologically plausible, involving neurotransmitter systems that are implicated in the aetiology of schizophrenia, such as glutamate, and inflammatory pathways of the immune system (Jia et al., 2010).

Whilst genetics play an important role in the aetiology of schizophrenia, the environment also appears to influence risk for the disorder. Trauma and adversity, including urbanicity (Pederson and Mortensen, 2001), childhood maltreatment (Sideli et al., 2012), and substance abuse, particularly cannabis (Bowers et al., 2001; Di Forti et al., 2015) are all associated with schizophrenia. More recently, research has focused

on how environmental factors act on genetic vulnerabilities in an interactive way to increase risk of psychosis (e.g. Krabbendam and van Os, 2005; Fisher et al., 2014; Uher, 2014). Similarly, investigations of interactions between the environment and biological vulnerabilities may shed light on the complex aetiological mechanisms underlying schizophrenia. For example, stressful life events may interact with underlying abnormalities in the biological stress response system (the HPA axis), increasing risk for psychosis further than each does alone (Mondelli, 2014; Ajnakina et al., 2014).

Therefore, a complex array of biological, genetic, and psychosocial risk factors likely act together to increase the risk of psychosis. The timing at which each factor exerts an influence probably differs. Early in development, genetics and obstetric complications may set up a predisposition or vulnerability. This vulnerability is likely further modified throughout development, sometimes influenced by trauma or adversity during childhood, leading to neurobiological alterations that further increase risk. Further risk factors during adolescence, including social anxiety, stress and isolation, and abuse of drugs, may place further strain on already disordered neurobiology.

Whilst many different factors may play a role in aetiology, one theory suggests that they lead to similar neurobiological dysfunction. Dysfunction within the dopamine system (discussed in detail in chapter 1.3) has been termed the ‘final common pathway’ on which various aetiological factors converge to produce the symptoms of psychosis (Howes and Kapur, 2009). The dopamine theory of schizophrenia has been incredibly influential in our understanding of the emergence of psychotic symptoms, and is supported by evidence from a variety of sources. Recent modifications to the theory consider the potential role of other neurotransmitters in the aetiology of schizophrenia, and potentially different patterns of underlying neurobiological dysfunction may help explain heterogeneity of outcome and response to treatment.

1.2. Neurobiological factors in schizophrenia aetiology

Whilst the precise aetiological mechanisms of schizophrenia remain unclear, research has revealed numerous underlying neurobiological alterations in individuals with the disorder. In particular, the dopamine system has been strongly implicated and the dopamine hypothesis remains the dominant theory regarding the neurobiological pathophysiology of schizophrenia.

1.2.1. The dopamine system

Dopamine is a catecholamine synthesised from tyrosine, which is obtained in the diet, and is a precursor in the synthesis of the other catecholamines (noradrenaline and adrenaline). Following its release into the synapse, dopamine is catabolised by monoamine oxidase (MAO) and catechol-O-methyl transferase (COMT) to form homovanillic acid (HVA). Reuptake occurs via energy-dependent Na+ cotransport at the dopamine transporter (DAT), found mainly in the extrasynaptic region of the axon terminal.

Dopamine is found throughout the brain, with cell bodies in the midbrain (e.g. substantia nigra and ventral tegmental area), hypothalamus and the olfactory bulb. Midbrain projections to the forebrain are extensive, with connections to the dorsal and ventral striatum, cortical regions (prefrontal cortex, anterior cingulate, perirhinal, and entorhinal cortices), and limbic regions (amygdala, lateral septum and hippocampus).

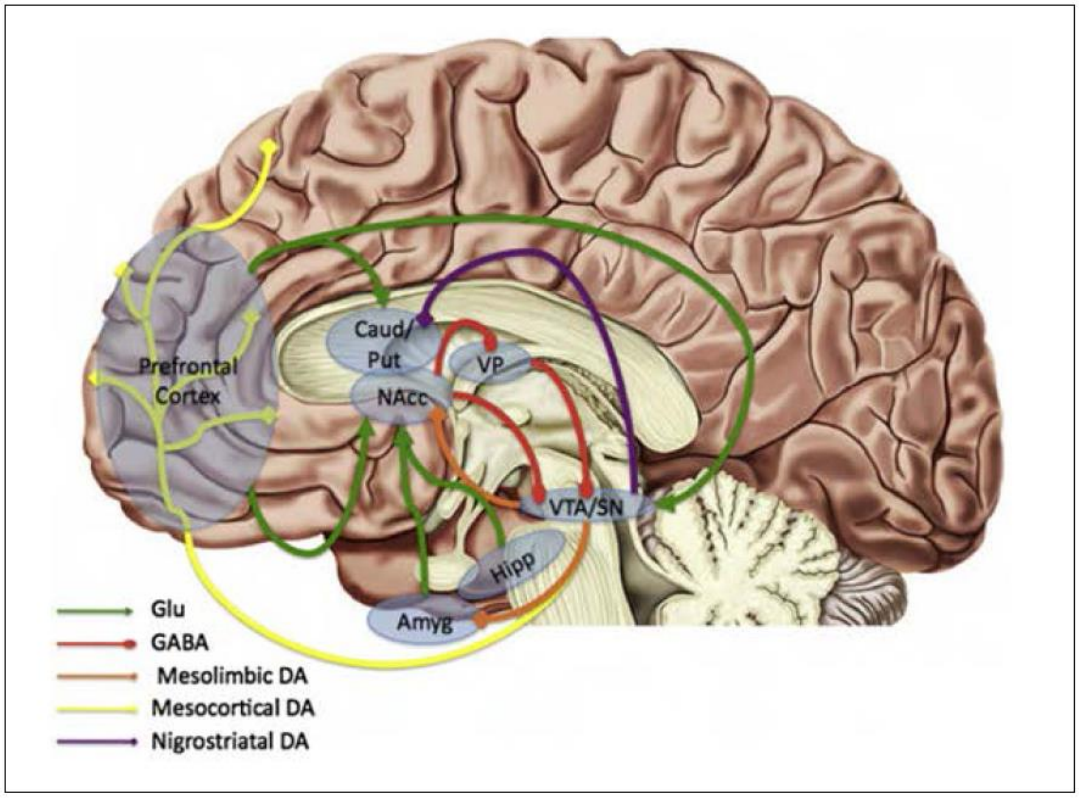

Figure 1: *Dopamine pathways in the brain*

Four main dopamine pathways are recognised: the mesolimbic, mesocortical, nigrostriatal, and tuberinfundibular pathways. (Adapted from Dichter *et al.* (2012)).

There are several important dopamine pathways (Figure 1), which have been attributed different functions.

- Mesolimbic: connecting ventral tegmental area (VTA) to nucleus accumbens, amygdala, hippocampus, and medial prefrontral cortex (PFC). The mesolimbic pathway is implicated in reward and reinforcement, and dysregulation in this pathway may underlie the positive symptoms of schizophrenia.
- Mesocortical: connecting VTA and frontal cortex. The mesocortical pathway is implicated in motivational and emotional responses, and dysregulation of this pathway may underlie the negative symptoms of schizophrenia.
- Nigrostriatal: connecting substantia nigra and striatum. The nigrostriatal pathway is implicated in motor control. It is thought that actions of antipsychotic

medications in this region underlie extra-pyramidal side effects and other motor disorders associated with the treatment of schizophrenia.

- Tuberinfundibular: connecting hypothalamus and pituitary gland. This system regulates prolactin levels. The effects of antipsychotics on this pathway are thought to lead to prolactin-related side effects, such as prolactinaemia.

Within these pathways, five types of dopamine receptors are found, which can be divided into two families according to their distribution, pharmacology, and the mechanism that follows receptor activation. The D1-like receptor family includes receptors D1 and D5, which are widespread through the brain including in the striatum, nucleus accumbens, limbic areas, and the thalamus. The D2-like family includes receptors D2, D3, and D4, which are found in the striatum (particularly D2), prefrontal cortex, cingulate, temporal cortex, entorhinal cortex, amygdala and ventral tegmental area. The hypothalamic D2 receptors in particular have been implicated in the action of antipsychotic medications and therefore hypothesised to be important in the pathogenesis of schizophrenia.

1.2.2 The dopamine hypothesis

The original dopamine theory suggested that schizophrenia resulted from a hyperdopaminergic state, primarily in the striatum and nucleus accumbens. The theory was founded in work that characterized dopamine pathways in the brain and the effects of antipsychotics on this neurotransmitter system (Carlsson and Lindqvist, 1963). Potential hyperdopaminergia was consistent with the observation that positive symptoms appeared to reduce following the administration of D2 receptor blockers (Angrist and Gershon, 1970). Furthermore, it was observed that the clinical dosage of antipsychotic drugs correlated with the degree of D2 receptor blockade they exhibited (Creese et al. 1976; Seeman and Lee 1975). Additionally, many drugs that increase dopamine levels (such as amphetamine) are associated with psychotic experiences (Tost et al., 2010). These observations, alongside others, lent support to the initial

formulation of the dopamine hypothesis by van Rossum in the 1960s (van Rossum, 1966).

However, there were some aspects of psychosis and its treatment that were not well explained by the original dopamine hypothesis. For example, whilst antipsychotics targeting D2 receptors reduced positive symptoms, they did not greatly affect negative or cognitive symptoms, and it appeared unlikely that these resulted from mesolimbic hyperdopaminergia. Furthermore, drugs that enhance dopamine signalling, such as amphetamine, led to exacerbations of symptoms in patients with psychosis at doses that did not induce psychosis in healthy individuals (Lieberman et al., 1987). These findings suggested that the pathophysiology underlying psychosis was more complicated than the original theory suggested and so the dopamine theory was reformulated (Davis et al. 1991). This reformulation posited that negative and cognitive symptoms resulted from dysfunction in D1 receptor signalling in the PFC. The theory posited that, rather than a global hyperdopaminergia, dopamine signalling was dysregulated, leading to hypodopaminergia in some regions, such as the PFC.

The reformulated dopamine theory was supported by preclinical studies illustrating the importance of D1 receptors in PFC function (Goldman-Rakic et al., 2000), as well as by functional imaging in humans showing altered PFC activation in schizophrenia (Knable and Weinberger, 1997). In particular, imaging suggests a role of D1 receptors in cognitive function in schizophrenia (Abi-Dargham et al., 2002). Molecular imaging techniques, such as positron emission tomography (PET) and single photon emission computed tomography (SPECT), provide further evidence. Such studies have reported increased dopamine function in schizophrenia, particularly the striatum (e.g. Laruelle et al., 1996; Abi-Dargham et al., 1998). However, some also probed prefrontal dopamine, showing an upregulation of D1 receptors in this region, which may signify a long-term dopamine deficit in this region (Abi-Dargham, 2003). Increased mesolimbic dopamine function may result from dysfunctional mesocortical dopamine function. In healthy individuals, normal cortical function inhibits subcortical dopamine via reciprocal

interactions between regions, such as the striatum and the PFC. In schizophrenia, this inhibition may no longer be present (i.e. there is disinhibition) due to a dysfunction of the mesocortical dopamine system. As a result, mesolimbic dopamine function may increase (Weinberger, 1987).

Therefore, rather than a simple hyperdopaminergic model, the current view is that dopamine signalling may be dysregulated, whereby subcortical (mesolimbic) signalling is increased and cortical (mesocortical) afferents to the PFC show reduced activation, resulting in positive and negative/cognitive symptom profiles, respectively.

1.2.3 The role of other neurotransmitters in schizophrenia

Whilst disrupted dopamine signalling has received the most attention in schizophrenia research, the importance of other neurotransmitter systems has more recently been recognised. A hypothesis of dopamine dysfunction is no longer thought sufficient to explain the symptoms of psychosis or the effect of antipsychotic medications to reduce symptoms. In particular, the role of serotonin and glutamate has received increasing attention. Indeed, it is becoming increasingly clear that each neurotransmitter system should not be considered in isolation. Rather, the disorder is likely determined by a complex pattern of changes within a number of neurotransmitter systems and brain regions.

1.2.3.1 Serotonin

Two major lines of research support the assertion that serotonin plays a role in the neuropathology of schizophrenia. Initially, it was observed that certain hallucinogens, such as LSD, elicit psychotic symptoms in healthy individuals (Paparelli et al., 2011). Serotonin was implicated in the action of LSD, with studies reporting direct agonist action at serotonin receptors in the central nervous system (Anden et al. 1968). More specifically, animal studies implicated the serotonin-2 receptor, as this subtype appeared to mediate the psychotomimetic properties of hallucinogens (Nichols, 2004).

The role of serotonin-2 receptors was further supported by post-mortem studies reporting reduced serotonin receptors in the prefrontal cortex in the brains of patients with schizophrenia (Mita et al., 1986).

The second major factor influencing theories of serotonin function in schizophrenia related to the development of the second-generation antipsychotics (SGAs). Whilst research with hallucinogenic drugs had implicated serotonin in schizophrenia, drugs that target serotonin alone do not treat the psychotic symptoms (Kapur and Mamo, 2003). However, the introduction of clozapine, and subsequent SGAs, suggested that serotonergic action complemented action at other receptors, including dopamine, to endow a substance with antipsychotic properties. More details regarding mechanisms of action of antipsychotic medications can be found in chapter 1.4 (page 29).

1.2.3.2 Glutamate

More recently, a potential role for glutamate in psychosis has been posited (Olney et al. 1999). This hypothesis is rooted in observations from the 1950s that drugs that target the NMDA receptor, such as phenycyclidine (PCP) and ketamine, have psychotogenic properties in humans, (Moghaddam and Javitt, 2012). Such substances not only induce positive symptoms, but also negative symptoms (Krystal et al., 1994). Whilst increased glutamate levels by ketamine increase associated psychotic symptomatology, the effects are ameliorated by antipsychotics, which act to reduce glutamate levels. This suggests that glutamate plays a role in response to antipsychotic treatment (Kargieman et al., 2008). Indeed, it is suggested that glutamate dysfunction, as opposed to dysregulation of other neurotransmitter systems, may underlie treatment-resistance in certain individuals (Stone et al., 2007).

Pharmacological evidence for a role of glutamate has been further supported by neuroimaging research. For example, single photon emission tomography has used tracers to show limited NMDA availability in the hippocampus is related to increased severity of symptoms (Pilowsky et al. 2006). Proton magnetic resonance spectroscopy

(1H-MRS) can probe glutamate levels in the brain and a recent study using this technique reported higher levels of glutamate in the anterior cingulate cortex of FEP, which was associated with increased scores on the PANSS negative symptom subscale (Egerton et al., 2012). However, whilst 1H-MRS has shown altered glutamate signalling, patterns of change are variable (Merritt et al., 2014). Therefore, neuroimaging evidence supports the presence of glutamatergic abnormalities in schizophrenia, but the precise patterns of pathophysiology and the mechanisms by which this relates to symptoms is yet to be elucidated.

1.3. Dopamine and the aberrant salience model of psychosis

The dopamine hypothesis of psychosis provided a partial explanation of the biological basis of psychotic symptoms, but did not account for the phenomenological experience of the disorder. To overcome this, Kapur (2003) proposed a framework that attempted to bridge the gap between the brain and the mind in psychosis. The framework drew on evidence that dopamine plays a role in reward processing and the attribution of salience to stimuli. Not only does such an account relate the phenomenology of psychosis to the biological dysfunctions reported in psychosis, it also can provide a framework to explain the effects of pharmacological treatment of the symptoms. The sections that follow outline the role of dopamine in reward and salience, before describing the aberrant salience hypothesis of schizophrenia. Lastly, the chapter outlines the measurement and investigation of aberrant salience in schizophrenia.

1.3.1 Reward and motivational salience

Pleasant or positively reinforcing stimuli are referred to as rewards or rewarding. However, a more accurate description would suggest that reward is a “composite psychological process requiring multiple brain systems” (Berridge and Kringelback, 2008, p20). Indeed, it is purported to consist of three components: ‘liking’ (the hedonic pleasurable experience of reward), ‘wanting’ (incentive motivational aspects of reward), and ‘learning’ (representations and associations related to rewarding or punishing stimuli based on past experiences) (Berridge and Kringelbach, 2008). Preclinical studies suggest opioid systems underlie the hedonic aspects of reward, whilst wanting and learning are associated with dopaminergic signalling. Here, the focus will be specifically on ‘wanting’ (i.e. motivational aspects of reward processing) in schizophrenia, and associated dopaminergic signalling.

Incentive motivational processes involve stimuli capturing attention and driving behaviour, whilst incorporating current physiological state and previously learned associations to determine context-appropriate behaviour (Berridge, 2012). This process

prioritises stimuli in the environment, such that limited cognitive resources can be appropriately allocated by focusing on the important components of what is generally a busy sensory environment. Stimuli that capture attention (salient stimuli) may be either internal or external, and once 'tagged' as important they drive the individual to either approach the stimulus, if this is rewarding, or avoid the stimulus, if it is punishing. Thus, salient stimuli capture attention, driving goal-directed thought and behaviour.

Research suggests that the importance or salience of stimuli is signalled by dopamine. Early animal research reported that when animals are implanted with electrodes in dopamine-rich regions, they self-stimulate repeatedly, in preference to food and sex (Olds, 1958). Further evidence for a role of dopamine in reward is derived from research on addiction. For example, a number of addictive drugs act to increase dopamine levels, potentially contributing to their ability to create dependence (Wise and Hoffman, 1992). Furthermore, separation of the neural substrates for the different components of reward implicate a specific role for dopamine in motivation for rewards. For example, dopamine depletion in the nucleus accumbens leads to decreased investigatory or instrumental responses, but does not affect consummatory responses in animals (Berridge and Robinson, 1998). Thus, a dopamine-depleted mouse will not work for access to food by pressing a lever, but if the food is freely accessible then the mouse will eat it. This suggests that dopamine mediates the 'wanting' (motivational) component of reward, but does not impact on the pleasurable aspects of a rewarding stimulus (the 'liking' components).

Seminal work by Schultz and colleagues (1997) showed recordings of dopamine neuron activation in response to environmental stimuli from individual cells in primates. Dopamine neurons showed phasic activation in response to unpredicted or novel rewards. However, when reward was fully predicted by a predictive stimulus (conditioned stimulus, CS+), dopamine was no longer released on presentation of the reward. Rather, the CS+ now elicited a phasic dopamine response (Schultz et al., 1997). Thus, mesocorticolimbic dopamine signalling may represent prediction (the

mismatch between expectation and receipt of a reward) rather than signalling reward per se. The size of a prediction error depends on several factors, including the uncertainty, magnitude, and timing of reward. Behaviour and cognition are adjusted according to the size of the dopamine response, which is determined by the size of the prediction error. A larger dopamine response signals a more salient stimulus, and increases the likelihood that it will direct attention and behaviour.

Dopamine may not solely signal reward, but is also implicated in aversive signalling, although this remains a topic of debate (Schultz, 2010). Phasic dopamine responses to aversive stimuli have been recorded in rats (e.g. Mantz, 1989), and some suggest that factors other than reward, like novelty, may be more important (Winton-Brown et al., 2014). However, novelty may be intrinsically rewarding, as animals have been shown to orient to both aversive and rewarding novel stimuli (Heinz et al., 2009).

In summary, dopamine has been implicated in the signalling of incentive motivational aspects of reward. Dopamine is released in a phasic manner in response to important, novel stimuli (or CS+). These signals ensure attention is paid to the stimuli (whether external or internal) and subsequently drive behaviour. The aberrant salience hypothesis, outlined in the next section, suggests that these processes may be altered in psychosis.

1.3.2 Aberrant salience hypothesis of psychosis

Whilst research has suggested that dopamine is dysregulated in psychosis, it was not previously clear how this related to the subjective experience of symptoms in the disorder. Any complete understanding of psychosis requires that neurobiological-level explanations of symptomatology are integrated with psychological and phenomenological descriptions of psychosis (Jensen and Kapur, 2009).

The aberrant salience hypothesis (Figure 2) was proposed as a framework to resolve this issue (Kapur, 2003). Motivational salience was posited as the intermediate process

connecting brain disturbances (specifically dopamine dysfunction) to symptoms, thus linking biological explanations with the psychological experience of the disease. The theory suggests that normal processes of attributing salience to stimuli, outlined above, are disrupted in psychosis because of abnormal dopamine signalling.

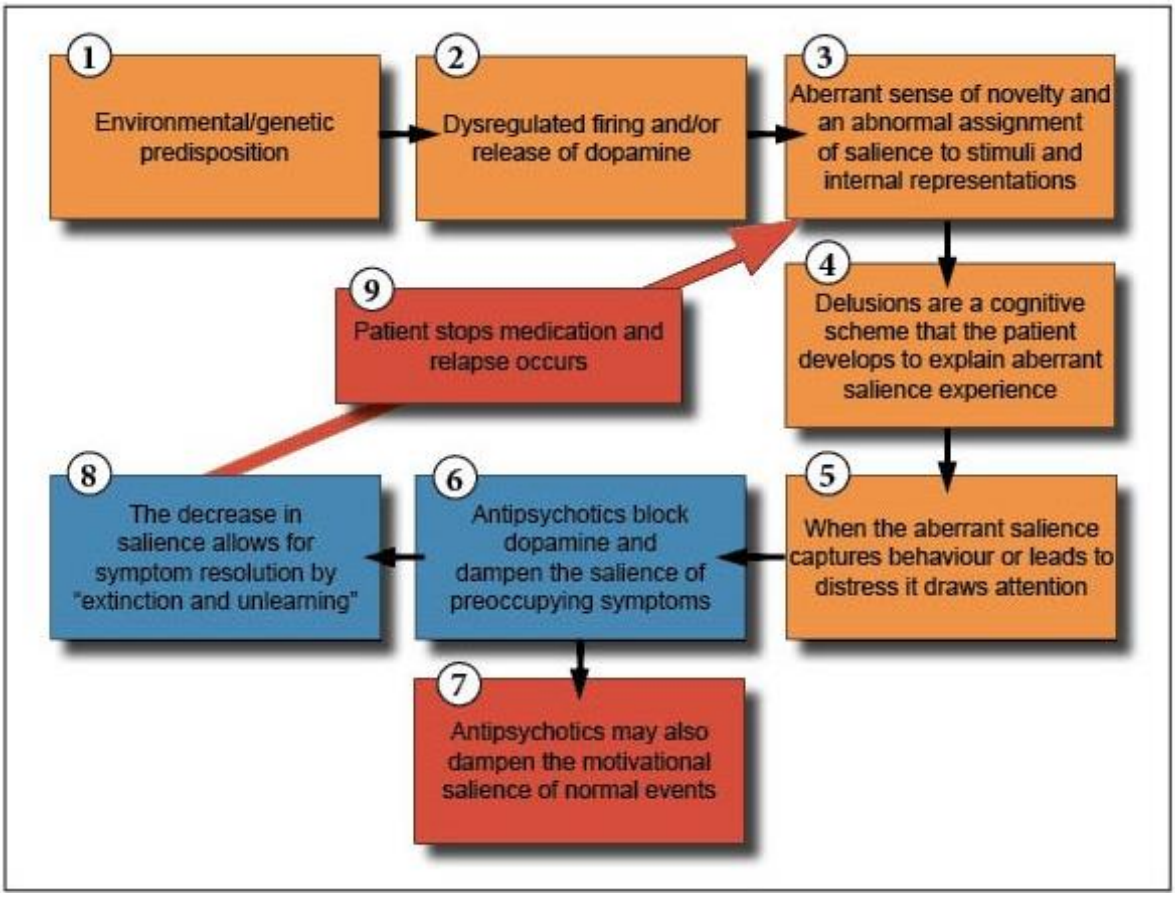

Figure 2: *The aberrant salience hypothesis*

Illustration of the aberrant salience theory, showing how symptoms develop due to altered dopamine signalling (orange), how antipsychotics affect these processes (blue), and the negative consequences of medication or stopping treatment (red). Numbers indicate the chronology of the events. (Adapted from Kapur et al., 2005).

The aberrant salience theory proposes that mistaken attributions can occur when dopamine signalling is disrupted, as this would in turn disrupt the normal processes of salience attribution. In a hyperdopaminergic state, phasic dopamine responses, which are normally elicited by important novel stimuli, would be elicited chaotically due to the disruption in dopamine firing (Kapur et al., 2005). This would lead to aberrant attribution of salience to neutral stimuli, such that irrelevant stimuli are imbued with significance

and meaning. Thus, neutral stimuli may attract attention, and influence behaviour and cognition inappropriately when associated with a dopamine burst, which 'labels' them as important. This has been termed "aberrant salience" (Kapur, 2003), and may underlie the positive symptoms of psychosis, particularly delusions (Roiser et al., 2009). Conversely, "adaptive salience" is the process of correctly attributing importance to stimuli that are novel or significant, for example if they are predictive of reward. Adaptive salience may too be disrupted in psychosis, leading to negative symptoms, such as amotivation, blunt affect, and withdrawal (Roiser et al., 2009).

The aberrant salience hypothesis is consistent with clinical reports of the experience of schizophrenia. In the prodromal period, accounts describe a subjective feeling of increased aberrant salience. Individuals have described a feeling that many stimuli begin to attract their attention and seem to hold significance, although they were previously unimportant. This 'delusional mood' does not constitute overt psychosis, and a further stage is required to understand how this develops into the delusions and hallucinations that characterise the disorder. Indeed, the presence of aberrant salience and its associated neural correlates have been observed in the general population, associated with subclinical psychotic symptoms (Van Os et al. 2009). Further, aberrant salience has been observed in people at ultra-high risk for psychosis, prior to transition to psychosis (Roiser et al. 2013).

To explain how experiences of heightened saliency develop into acute psychotic symptoms, impairments in reasoning may also be necessary. This framework has been particularly applied to the development of delusions. Howes and Kapur (2009) suggested that delusions arise when an individual attempts to explain their unusual subjective experiences of heightened saliency. They are therefore the explanations that an individual develops to understand the experienced importance in connection to previously ignored stimuli. This is consistent with the idiosyncratic nature of delusions, as people incorporate their experiences and culture into their explanations. It may also serve to explain the development of hallucinations, in which salience is aberrantly

attributed to internal representations of memories and percepts (Kapur, 2003). Furthermore, the feelings of threat and anxiety related to these sorts of experiences may be associated with dopamine dysfunction in limbic regions such as the amygdala (Pankow, 2012).

Antipsychotic medications have also been incorporated within the salience attribution framework. Kapur (2003) proposed that the 'shared psychological effect' of all antipsychotics was to dampen salience through the dopamine antagonism that reverses hyperdopaminergia underlying psychotic symptoms. Rather than acting directly on thoughts or ideas therefore, antipsychotics simply alter dopaminergic signalling, producing a context in which new aberrant salience attributions are less likely to form, and in which previously formed attributions are able to extinguish. This is consistent with subjective reports that following treatment delusional beliefs decrease in their significance and importance, and so have less influence on daily function (e.g. Winkleman, 1954, cited in Kapur, 2003). In addition, relapse often occurs when antipsychotic treatment is stopped, consistent with a model in which the return of dysregulated dopamine signalling reintroduces a context in which aberrant salience attributions are more likely to form (Gitlin et al. 2001). Thus, treatment may temporarily dampen salience associated with disrupted dopamine but does not fundamentally alter the pathophysiology underlying psychosis.

Whilst the salience attribution theory can effectively explain the mechanisms by which dopamine dysfunction leads to positive symptoms (particularly delusions), it is less able to account for the origin of negative and cognitive symptoms. It is possible that dopamine dysfunction plays a role in symptoms such as avolition and anhedonia. Here, hypodopaminergia would lead to a failure to assign importance to novel and important stimuli (i.e. a failure of adaptive salience). Furthermore, antipsychotic treatment can produce a 'deficit-like syndrome', which may be caused by a further dampening of adaptive salience attribution (Kapur, 2003). As described above, neurotransmitters other than dopamine may also play a role, particularly glutamate, which interacts with

dopamine in complex and still not entirely understood ways. Further work is required to elucidate the mechanisms by which neurotransmitters interact with one another, and how this might relate to the processes of salience attribution.

1.3.3 Measuring salience

Various methodologies have been used to investigate motivational salience processes. Many studies have used classical conditioning paradigms, the most widely used of which is the monetary incentive delay task (MID) (Knutson et al. 2001). In this task, reaction times to cued targets determine rewards, with several trial conditions usually composed of certain or uncertain outcomes (a gain, neutral or a loss). The task can provide behavioural indices of reward processing in the form of hit rates or reaction times, as well as neural activation associated with reward anticipation and receipt. Other methods have also been used to investigate reward learning and its importance in schizophrenia, such as associative causal learning tasks (Corlett et al. 2004) and cued-reinforcement reaction time tasks (Murray et al. 2008).

The task that will be used in this thesis, the Salience Attribution Task (SAT), was developed by Roiser and colleagues (2009) to specifically probe motivational salience. The SAT is a speeded-response task with monetary rewards, providing measures of adaptive and aberrant salience (full details provided in Methods, page 109). Four stimuli are used, characterized by colour and form, with the probability of reinforcement dependent on just one of these (task-relevant), but not the other (task-irrelevant). By comparing the responses for the task-relevant and task-irrelevant dimensions, measures of adaptive and aberrant motivational salience can be estimated.

Adaptive salience within this paradigm is defined as the ability of an individual to differentiate between low and high probability cues, and attach importance to stimuli predictive of reward. Aberrant salience provides a measure of whether participants erroneously differentiate between cues that are equally associated with reward, such that importance is attributed to a neutral cue. Both of these measures are assessed by

reaction times (implicitly) and a visual analogue scale (explicitly). Unlike studies using the MID, the SAT specifically tests salience attributions, and can provide behavioural and neural measures of both aberrant and adaptive salience processes. This is an advantage in studies of schizophrenia, because both adaptive and aberrant salience processes may be altered in the disorder and this may be seen at both behavioural and neural levels, as I will outline in the following sections.

1.3.4 Studies of salience attribution

Since the aberrant salience theory was proposed, several studies have investigated salience attribution and reward processing using behavioural and fMRI paradigms. In the following sections, I outline the evidence for abnormalities in reward processing of individuals with psychosis. Studies are organised according to the patient population in which they were carried out (prodromal, drug-naïve/unmedicated psychosis, first episode psychosis, and chronic schizophrenia) to illustrate the abnormalities seen at different stages in the course of schizophrenia.

1.3.4.1 Studies in patients with chronic schizophrenia

Studies investigating neural activation underlying incentive salience processing in chronic, medicated patients with schizophrenia consistently report abnormalities in striatal, hippocampal, and frontal regions (Koch et al., 2010; Walter et al., 2009; Simon et al., 2010; Waltz et al., 2010; Diaconescu et al., 2011; Gradin et al., 2011/2013; Dowd and Barch, 2012; da Silva Alves et al., 2013). Whilst similar networks of regions are activated in anticipation of, or response to, reward in patients, certain regions show decreased activation compared with healthy controls. For example, Gradin and colleagues (2013) reported activation in the striatum, amygdala-hippocampal complex, and midbrain of healthy controls, and functional connectivity between the insula and anterior cingulate cortex during reward learning. In patients, activation was detected in the insula and anterior cingulate cortex, but not in the other regions. Moreover, the same study reported reduced functional connectivity between the insula and anterior

cingulate. In a study of 10 patients with schizophrenia and 12 healthy controls who underwent two scans during the MID task, lower activation in patients compared with healthy controls in the superior temporal cortex and posterior cingulate was reported during reward anticipation (da Silva Alves et al., 2013).

The specificity of salience processing deficits to schizophrenia is not clear, but is supported to some degree by studies comparing different disorders. Comparing instrumental reward learning in patients with schizophrenia or depression versus healthy controls, abnormalities have been reported in patients with both disorders (Gradin et al., 2011). However, the patterns of abnormality differed. In depression, there was reduced prediction error related to anhedonia in the striatum and midbrain. In schizophrenia, prediction error signals were reduced in the caudate, thalamus, insula and amygdala-hippocampal complex, with the degree of disruption correlated with positive symptom severity, but not negative symptoms.

Elsewhere, the lack of differential activation in patients with chronic schizophrenia to high, neutral or low probability rewards has been noted. A study of 17 patients with schizophrenia and 17 healthy controls completing the MID task found that whilst healthy controls showed greater activation for gains compared with losses in medial prefrontal cortex (PFC), temporal cortex, and the amygdala, activation in patients failed to differentiate between these (Waltz et al., 2010). Similarly, Koch and colleagues (2010) reported that whilst fronto-parietal activation in healthy controls reduces as the predictability of stimuli improved, this was not seen in patients. Another study found that both patients and healthy controls explicitly acquired conditioning during an appetitive conditioning paradigm with monetary rewards, with activation in the striatum, hippocampus, and PFC in response to the CS+ (Diaconescu et al., 2011). However, patients also activated these regions in response to the CS-, showing an inability to differentiate between rewarded and unrewarded stimuli. Furthermore, galvanic skin recordings showed that patients (unlike controls) did not implicitly differentiate between the CS+ and the CS-.

One study failed to find any differences between patients with schizophrenia and healthy controls (Simon et al., 2010). However, all 15 patients were treated with an SGA, which may act to 'normalise' neural activation underlying salience processing. Nonetheless, the authors reported a negative correlation between ventral striatal activation during reward anticipation and symptoms of apathy in the patients. Another study found no significant differences between activation in 16 olanzapine-treated patients with schizophrenia and 16 healthy controls in the ventral striatum, ventral tegmental area, and the anterior cingulate cortex during reward expectation (Walter et al., 2009). However, anterior cingulate activation increased with increased probability of reward in healthy controls only and activation in this region in patients was negatively correlated with positive symptoms.

1.3.4.2 Studies in patients with first episode psychosis

Studies in patients with chronic schizophrenia are subject to several confounders, including illness duration and antipsychotic treatment. Progressive functional deterioration over illness course may influence reward processing and so studies have investigated early stages of the disorder (Corlett et al., 2007; Murray et al., 2008; Roiser et al., 2009), albeit still in medicated patients .

In a study of first episode psychosis (FEP) patients, Corlett and colleagues reported reductions in activation of right PFC when expectations were violated, the degree of which was related to delusions. Results from Murray and colleagues (2008) support other studies where patients failed to differentiate between high probability and neutral or low probability reward cues. Lower activation was found in patients compared with healthy controls in the midbrain, striatum, and limbic regions in response to high probability cues. Activation in these same regions was higher in patients compared with healthy controls in response to neutral cues. Similarly, there was a behavioural trend for patients to respond in a similar way to high probability as they did neutral cues, rather than increasing reaction times to high probability cues as expected.

In a behavioural study using the SAT, first episode psychosis patients exhibited decreased adaptive salience compared with healthy controls, but comparable levels of aberrant salience (Roiser et al., 2009). However, higher levels of aberrant salience were related to delusions within the patient group. A later study using fMRI to study salience processing in a group of healthy controls during the SAT (Roiser et al., 2010) reported activation in a network of structures associated with salience attribution, including the VTA, thalamus, ventral striatum, and PFC. Thalamic and PFC activation levels were related to adaptive salience in these healthy participants. Interestingly, the dorsolateral PFC and the medial temporal gyrus responded differentially to cues that were rewarded equally, but only where participants responded to them as if they were differentially rewarded (i.e. aberrant salience attribution). In those with greater aberrant salience, when responding to cues incorrectly (as if they were differently associated with reward), greater activation in the dorsolateral PFC and less activation in the medial temporal gyrus was seen (Roiser et al., 2010). Thus, brain regions responsible for incentive motivation processing erroneously differentiate between cues that are not differentially rewarded, and this is associated with behavioural aberrant salience.

1.3.4.3 Studies in antipsychotic-naïve or unmedicated patients with psychosis

Studies in medicated patients are confounded by the effects of treatment, complicating interpretation. To dissect the effects of antipsychotic medication from alterations primary to the disease pathophysiology, studies have investigated reward processing in antipsychotic-naïve or unmedicated patients with psychosis (Juckel et al., 2006a; Schlagenhauf et al., 2009; Esslinger et al., 2012; Nielsen et al., 2012). This can reveal changes that are present in the disorder, prior to any medication effects.

All studies in unmedicated patients reported lower activation in the ventral striatum in response to reward-indicating cues (Juckel et al., 2006a; Esslinger et al., 2012; Nielsen et al., 2012) or during successful versus unsuccessful loss avoidance (Schlagenhauf et al., 2009). This supports the existence of reward-processing abnormalities in psychosis

before antipsychotic treatment commences.

The largest of these studies compared activation during a MID task in 31 antipsychotic-naïve patients and 31 healthy controls, reporting reduced activation to salient cues, not only in the ventral striatum, but also in the ventral tegmentum, and anterior cingulate cortex (Nielsen et al., 2012). However, only reduced activation in the ventral striatum was correlated with positive symptom scores. Altered ventral striatal activation has been shown to relate to positive symptoms in another study comparing 27 unmedicated patients and 27 healthy controls (Esslinger et al., 2012). Furthermore, a relationship between delusional psychopathology and activation in the medial PFC has been reported elsewhere (Schlagenhauf et al., 2009), where smaller differences in activation between successful and unsuccessful loss avoidance related to higher delusional scores.

Conversely, Juckel and colleagues (2006a) reported an association between reduced left ventral striatal activation and negative symptom severity, although there was also a trend to a correlation with positive symptoms. However, this was in a small group of just 10 patients, some of whom had been previously medicated.

1.3.4.4 Studies in subclinical or at risk groups

Whilst studies in antipsychotic-naïve or unmedicated psychosis suggest that altered reward processing is present early in the disorder prior to antipsychotic treatment, studies in ultra-high risk (UHR) individuals, schizotypy, and first-degree relatives suggest that abnormal salience attribution can be detected even before onset of frank psychosis. This may suggest that abnormal salience processing plays a role in the aetiology of the disorder or may be a risk factor in itself.

Using fMRI and [^{18}F]fluorodopa positron emission tomography (PET), 18 unmedicated UHR individuals and 18 healthy controls were assessed for neural activation during the SAT task and for dopamine synthesis capacity (Roiser and colleagues 2013). Higher

levels of aberrant salience in UHR correlated with delusional symptomatology and were associated with ventral striatal activation to irrelevant stimulus features. There was also a negative relationship between striatal dopamine synthesis capacity and hippocampal activation to irrelevant stimuli features, whilst the relationship was positive in controls. These findings were consistent with those of another study in UHR individuals reporting a trend to decreased ventral striatal activation compared with healthy controls during a MID task (Juckel et al., 2012).

Similarly, a study of non-psychotic individuals with schizotypal beliefs reported prediction error abnormalities in striatal and frontal regions (Corlett et al., 2012). Individuals who did not learn appropriately about the predictive cues (and so found violations of predictive relationships less surprising) had reduced striatal prediction error activation. Reduced activation was related to schizotypal beliefs and the degree of associated distress. Furthermore, decreased ventral striatal activation to reward-indicating cues has been shown in first-degree relatives of patients with schizophrenia (Grimm et al., 2014). This suggests that such abnormalities form part of the risk for psychosis, but other factors play a role in the development of the disorder.

1.3.5 Chapter summary and conclusions

The reward and salience literature supports the assertion that salience attribution and reward processing are disrupted in psychosis. Studies in chronic patients show reduced activation in reward regions, such as the striatum, hippocampus and anterior cingulate cortex. Additionally, activation differentiating between high probability and neutral reward cues is not seen in patients, as it is in healthy controls. It seems that patients do not correctly assign importance to cues to reflect how often they are associated with reward. This is consistent with the aberrant salience hypothesis, in which patients are purported to attribute salience inappropriately to neutral stimuli.

FEP studies corroborate with these findings, suggesting that the effects of prolonged illness are not solely responsible for differences seen between patients and healthy

controls. Furthermore, studies in patients who are unmedicated or antipsychotic-naïve similarly show reduced activation in regions underlying reward processing, particularly the ventral striatum. The aberrant salience theory would predict abnormalities in regions of disrupted dopaminergic signalling in psychosis, such as the ventral striatum, which forms part of a cortico-ventral basal ganglia network of dopamine-rich structures and associated projection sites (Haber, 2011).

Results in patient studies suggest that rather than simple hypo or hyperactivation in response to reward cues, it is the appropriateness of activation that is important, i.e., differential activation for high, neutral, and low probability cues. This is consistent with the revised dopamine hypothesis, which suggests chaotic, dysregulated dopamine firing in psychosis, rather than simple hyperdopaminergia in the mesolimbic dopamine pathways. It is possible that antipsychotics act to dampen salience by reducing dopamine levels in the mesolimbic system, in turn reducing the 'noise' in this pathway and allowing phasic dopamine responses to important stimuli to signal salience appropriately.

Finally, findings from UHR individuals, individuals with schizotypy, and first-degree relatives, suggest that abnormalities in reward processing and salience attribution are present prior to treatment with antipsychotic medications, and may confer a degree of risk in developing the disorder. These alterations may relate to underlying alterations in dopamine signalling. Disentangling the effects of chronic disease treated with antipsychotics from those that are primary to the disorder is an important test of the aberrant salience hypothesis, which would suggest that abnormalities are present prior to and independently of treatment. UHR were also reported to have unimpaired adaptive salience (i.e., they are able to discriminate high and low probability rewards). However, decreased adaptive salience has been reported in patients (Roiser et al., 2009). This may reflect an effect of antipsychotics, which in the original aberrant salience hypothesis were proposed to dampen mesolimbic dopamine, which would alter both aberrant and adaptive salience levels. Furthermore, investigating how altered

reward processing in UHR relates to later transition to psychosis is key to understanding the aetiology of schizophrenia. This could inform preventative management techniques, perhaps allowing treatment prior to onset of frank psychotic symptoms, avoiding many adverse effects on function associated with an acute psychotic episode.

The current project offers a unique opportunity to assess salience attribution in a group of minimally treated/antipsychotic-naïve patients. This provides a test of the aberrant salience hypothesis, by investigating whether abnormal salience attribution is present at first episode, prior to treatment. The project will additionally assess the ability of salience to change with treatment, by looking at the longitudinal effects of medication on measures of salience attribution and in relation to response to treatment. Understanding the changes induced by current medications on salience processing will help us to elucidate mechanisms of successful treatment and potentially identify new treatment targets.

1.4 Antipsychotic medication

1.4.1 Treatments for psychosis

Prior to the 1950s, various biological and pharmacological treatments were used in attempts to treat the symptoms associated with schizophrenia, including prescribing cocaine, manganese or castor oil, and inducing coma through hypoglycaemia (Lehmann and Ban, 1997). Such treatments were rarely efficacious and often risked severe side effects. The serendipitous discovery of the antipsychotic effect of chlorpromazine in the 1950s dramatically altered the treatment of schizophrenia. The discovery that this antihistamine compound had antipsychotic effects when administered to patients with schizophrenia catalysed vast improvement in disturbed behaviour on psychiatric wards, and fuelled research into drug development for other psychoactive substances (Ban, 2007).

Today, several antipsychotic medications are available for prescription in the treatment of schizophrenia. They are generally divided into typical or first-generation antipsychotics (FGAs), and atypical or second-generation antipsychotics (SGAs). Despite variation in mechanisms of action, the dopamine system appears to be a common therapeutic target for all currently prescribed antipsychotics.

Chlorpromazine was the first of the FGA class, which includes flupenthixol, haloperidol, thiothixene, and zoclopenthixol, many of which are potent D2 receptor blockers (antagonists). FGAs are more associated with extrapyramidal side effects, other motor side effects (such as tardive dyskinesia and akathisia), and hyperprolactinaemia than are SGAs (Gardner et al., 2005). Whilst generally accepted to reduce positive symptoms associated with schizophrenia, FGAs appear to have little effect on negative or cognitive symptoms in the disorder (Gardner et al., 2005). Nonetheless, it is increasingly recognised that these symptom domains are central to the disorder, and that their treatment is a desirable and necessary component of recovery.

SGAs differ from FGAs by effecting reductions in positive symptoms, alongside a reduced risk of extrapyramidal side effects. The first of this class was clozapine, which remains the most efficacious treatment for patients who have shown poor treatment response to other antipsychotic medications (Mcilwain et al., 2011). However, the risk of life-threatening side effects, such as agranulocytosis, has restricted the use of clozapine. Several other SGA were subsequently introduced, including aripiprazole, amisulpride, quetiapine, and risperidone, which are more commonly prescribed in practice.

It is possible that the use of pharmacological agents to treat psychotic symptoms associated with schizophrenia has facilitated the implementation of community-based clinical care, although other political and economic reasons also likely played a role (Ban, 2007). Nonetheless, despite the reported efficacy of these drugs, their mechanisms of action are not fully elucidated, perhaps partly due to the complexity of their pharmacological mechanisms. Furthermore, as mentioned earlier in this thesis, there is a consistent proportion of patients in whom existing antipsychotics do not alleviate symptoms.

1.4.2 Mechanisms of action

1.4.2.1 First generation antipsychotics

The primary site of action for FGAs is the dopamine D2 receptor, with the majority exhibiting D2 antagonism (Stahl, 2013). As outlined in Section 1.2.1, page 7, several dopamine pathways exist throughout the brain. FGA action on these different pathways determine both the antipsychotic efficacy and the associated side effects of the compounds.

One key site of antipsychotic action is the D2 receptor within the mesolimbic pathway, which is posited by the dopamine theory as the source of positive psychotic symptoms resulting from excess dopamine. D2 antagonism here blocks the binding of dopamine

with D2 receptors, leading to an effective decrease in dopamine hyperactivity. Action within the mesolimbic pathway may also lead to a worsening of negative symptoms. For example, the mesolimbic pathway is associated with ‘pleasure’ or ‘reward’ in the normally functioning brain. D2 blockade might therefore block mechanisms of reward and reinforcement, leading to anhedonia, apathy, and amotivation.

However, FGAs are not selective for the mesolimbic system, as D2 receptors are found across the other dopaminergic pathways. Action at other sites underlies side effects associated with this class of drug. For example, cognitive symptoms experienced by many individuals diagnosed with schizophrenia may be worsened by FGA treatment due to blockade of D2 receptors in the frontal cortex (part of the mesocortical dopamine pathway). Extra-pyramidal side effects and other movement disorders are commonly associated with FGAs. These side effects mimic the symptoms of Parkinson’s disease (such as bradykinesia, stiffness, and tremor) and result from D2 blockade in the nigrostriatal pathway, which forms part of the extrapyramidal nervous system. Prolonged blockade of the nigrostriatal system can lead to tardive dyskinesia. This disorder is characterised by abnormal, involuntary facial and tongue movements, such as grimacing and tongue protrusion. It is thought that chronic nigrostriatal D2 blockade leads to upregulation and receptor supersensitivity. Whilst early removal of treatment can allow a reversal of tardive dyskinesia, continued treatment can cause the problem to become irreversible, even after the treatment is discontinued. Lastly, D2 receptor blockade in the tuberinfundibular pathway can lead to hyperprolactineamia, particularly in women in which it can interfere with menstruation and fertility.

FGAs cause D2 blockade at similar levels throughout the brain, and the degree of binding at particular sites determines whether therapeutic or adverse effects are experienced. Roughly 80% of D2 receptors in the mesolimbic pathway must be occupied for an individual to experience therapeutic effects (Stahl, 2013). However, in the dorsal striatum an occupancy of above 80% leads to motor side effects. Thus, a balance must be achieved between these two thresholds to achieve maximal

therapeutic effect without intolerable side effects (Figure 3). For FGAs, this therapeutic window is narrow, with a high risk of side effects at a dose necessary to pass the therapeutic threshold.

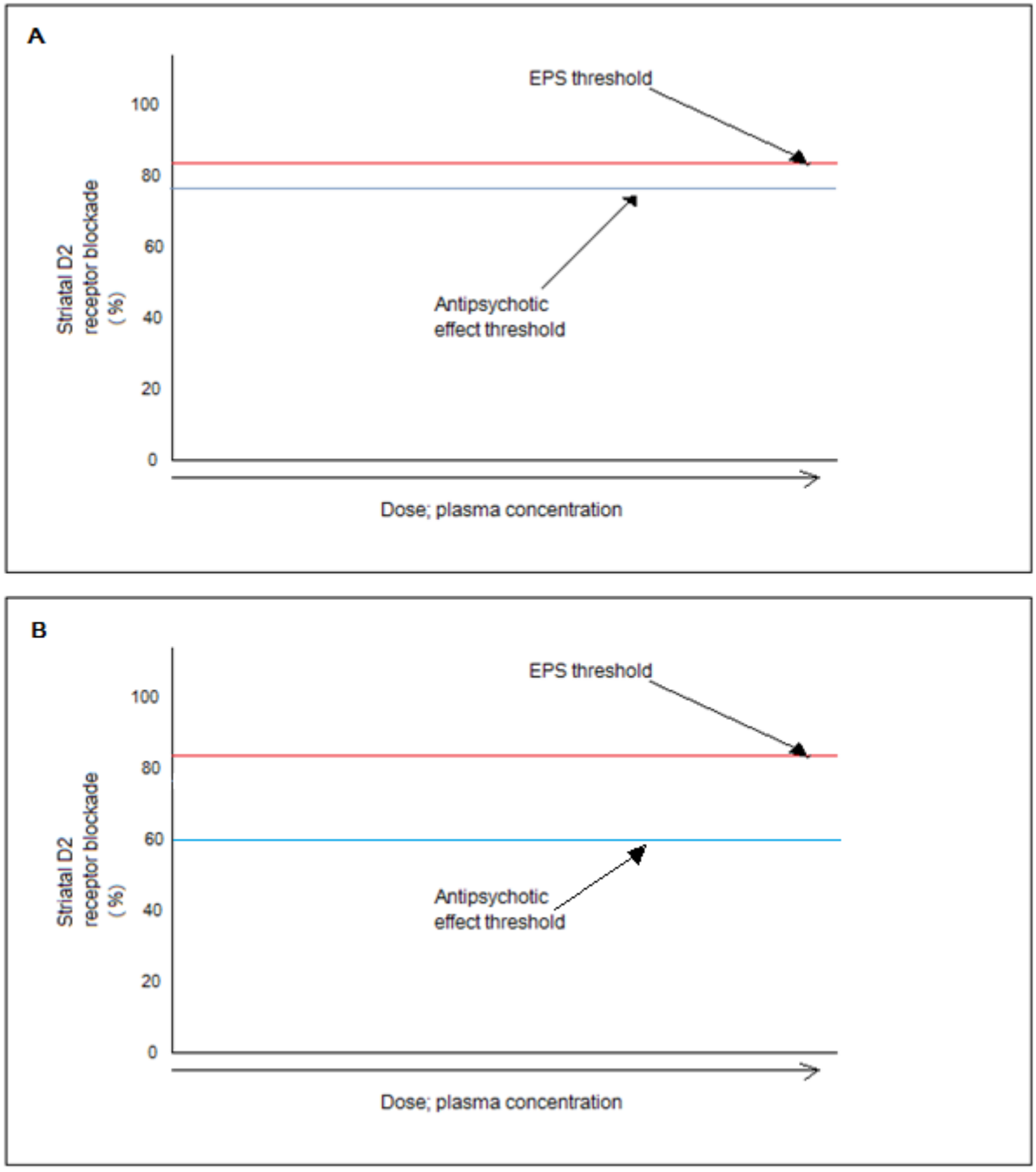

Figure 3: *Therapeutic window offered by A) FGAs and B) SGAs*

Treatment with antipsychotics must balance the therapeutic effects with the side effects. A) With FGAs, simple dopamine D2 receptor antagonism means that the thresholds for each of these are close, giving a narrow window within which an optimal balance can be found. B) With SGAs, D2 receptor antagonism is balanced by 5-HT_{2A} antagonism, which eases side effects and widens the therapeutic window. This ensures antipsychotic efficacy with a lower risk of side effects occurring. (Adapted from Stahl, 2013).

1.4.2.2 Second generation antipsychotics

Like FGAs, many SGAs have D2 antagonistic properties, from which it is thought antipsychotic efficacy arises. However, in addition to these properties, they have broader receptor profiles, with action at serotonin (5-HT) receptors. Interactions with 5-HT, in particular 5-HT_{2A}, receptors may account for the reduced risk of side effects that are typically associated with FGAs. In fact, the ability of an antipsychotic to reduce positive symptoms with a low risk of extra pyramidal side effects or hyperprolactineamia is loosely what classifies a drug as a SGA (Stahl, 2013). Due to these properties, they are often preferred over FGAs.

Serotonin is a neurotransmitter found throughout the brain. It is synthesised from tryptophan and taken up into synaptic vesicles before use in neurotransmission. Numerous 5-HT receptor types exist, the most important in this context being the 5-HT_{2A} type. 5-HT_{2A} receptors are postsynaptic and found in many brain regions, including parts of the neocortex such as prefrontal and parietal regions. These receptors enable downstream modulation of dopamine in the striatum, via effects on glutamate signalling. Serotonin enhances glutamate in the brainstem, leading to GABA release, which is inhibitory and reduces dopamine release in the striatum. Thus, the effect of SGA antagonism at 5-HT_{2A} receptors is disinhibition of dopamine, as the inhibiting action of serotonin via glutamate and GABA is itself inhibited. This action on dopamine may reduce the risk of extra pyramidal side effects. Furthermore, direct and indirect action of serotonin on the nigrostriatal and tuberinfundibular pathways further eases side effects seen with FGAs.

The more complex and nuanced modulation of dopamine levels by SGAs likely underlies their ability to treat psychotic symptoms whilst avoiding side effects by balancing D2 antagonism with 5-HT_{2A} antagonism. Furthermore, the degree of D2 and 5-HT_{2A} antagonism differs across brain regions. There is decreased dopamine in the mesolimbic pathway reducing positive symptoms, and disinhibited dopamine in the

nigrostriatal and tuberinfundibular pathways, lessening side effects. Competition between these mechanisms and regional differences allows dopamine receptor blockade to remain between 60–80% (depending on brain region) and thus reduces the antipsychotic effect threshold. This provides a larger therapeutic window than is possible with FGAs (Figure 3).

1.4.2.3 Amisulpride

Most patients included in the study that will form this thesis were prescribed amisulpride to treat psychotic symptoms as part of the OPTiMiSE clinical trial (see Methods, page 109). Amisulpride is a SGA, used to treat psychosis in schizophrenia and bipolar disorder, as well as dysthymia at lower doses. Amisulpride has effects on the dopaminergic and serotoninergic systems, with highest affinity for the D2 receptor, although it also acts as a D3 antagonist with lower affinity. It is usually prescribed at doses of between 400 – 1200mg/day for psychotic symptoms. At this dose, the drug has postsynaptic effects, inhibiting dopaminergic neurotransmission.

Amisulpride has been shown to be as effective as risperidone, haloperidol and other common antipsychotics, predominantly decreasing positive symptoms of schizophrenia but also showing an effect on negative and affective components of the illness (Curran and Perry, 2002). The choice of amisulpride in the current project was made on the basis of its relatively selective action on the dopamine system, and low affinity for other neurotransmitters thus simplifying interpretation of its effects.

1.4.3 Efficacy

There is some evidence that SGAs offer benefits over FGAs. At times, SGAs have been proposed to offer greater efficacy, particularly for cognitive and negative symptoms, and to give greater improvements in functioning and quality of life, as well as fewer extra-pyramidal side effects than FGAs (Miyamoto et al., 2005). However, meta-analysis suggests that this is not true of all SGAs, although amisulpride,

clozapine, olanzapine, and risperidone do all appear to show greater efficacy than FGAs (Leucht et al., 2009). Further, Leucht and colleagues (2009) did not find any specific benefit for SGAs in their efficacy to treat negative symptoms. There do seem to be benefits regarding reduced extra-pyramidal side effects, but other side effects such as weight gain and sedation can be more problematic for patients prescribed SGAs.

A more recent meta-analysis by the same group pooled data from 212 trials (comprising 43,049 patients) and found all drugs to be more effective than placebo, but that the traditional division between FGAs and SGAs was not necessarily supported (Leucht et al., 2013). They suggested that different drugs offer benefits in different domains, regardless of generation. Therefore, treating clinicians should consider these different domains in choosing drugs for individual patients, dependent on needs.

This brings greater individualisation to the prescription of antipsychotic medications, but it does not go far enough in offering tailored or personalised treatments. Some degree of trial and error is likely still required to find the optimal treatment for each individual. It would be more beneficial to be able to choose a drug based on need, using underlying biological factors to predict likely response and side effects. A better understanding of the effects of individual antipsychotics, their mechanisms of action, and the biological markers associated with response is therefore necessary.

1.4.4 Current treatment guidelines

Treatment guidelines in the UK are available from the National Institute for Health and Care Excellence (NICE), British Association of Psychopharmacology (BAP) and in the Maudsley Prescribing Guidelines. NICE guidelines for the treatment of schizophrenia (NICE, 2014) provide recommendations for the management and care of those diagnosed with this disorder within the psychosis pathway, under the section of psychosis and schizophrenia in adults.

These recommendations stress the need for early intervention in the disorder, with the choice of antipsychotic for a first episode based on collaborative consideration by the patient and clinical professional of the risks and benefits of the drug concerned. This includes consideration of metabolic, extrapyramidal, cardiovascular and hormonal side effects. Clozapine is recommended as a choice to be considered following the unsuccessful trial of at least two other antipsychotics at adequate doses, one of which must have been another SGA.

1.4.4.1 Early Intervention in Psychosis

In recent decades, many medical research fields have moved from focusing on curative treatments to preventative interventions. Intervening early is likely beneficial to both patients and society, reducing the overall cost of treatment, as well as the impact on the life and health of the patient, preventing the development of chronic, long-term disability. In psychiatry, a similar move to early intervention has occurred, although its application to psychosis has developed only in the last decade (Christy et al., 2014). Studies suggest that intervening during a 'critical period' with both pharmacological and psychological therapies may lead to better long-term outcomes (Birchwood et al., 1998). Longer duration of untreated psychosis (DUP) has previously been associated with poorer outcome (Bottlender et al., 2003), reinforcing the idea that intervening early in the disorder could improve prognosis, although whether these effects are substantial or sustained remains unclear (Marshall and Rathbone, 2011).

Initially, development of services for early intervention in psychosis occurred in Australia and the USA. However, the UK Department of Health recognised the need for early identification, assessment, and phase-specific treatment (DoH, 1999) and NICE guidelines on schizophrenia recommended their implementation across England and Wales (NICE, 2002). The NHS planned numerous services across these regions, and as of 2010, 145 such services were operating across the UK (Bird, 2010). Current

NICE guidelines recommend that early intervention is accessible to all those with first episode psychosis (NICE, 2014).

Whilst early detection and treatment may be beneficial for long-term outcomes, success is limited by the treatments available. For example, even if disorder is identified early in course, time might be wasted trialling numerous different antipsychotics. Individuals with psychosis do not always respond to the first antipsychotic tried, and may have to trial several in order to find one that is effective, with up to 40% not responding to their first treatment (Barnes et al., 2011; see also chapters 1.6 and 1.7). It would therefore be beneficial if one could predict treatment response before an antipsychotic is tried, and choose based on the underlying neurobiological pathology seen in individual patients. This would allow the implementation of *effective* early intervention, hopefully preventing much of the disruption and disability caused by poorly managed symptoms.

1.5 Neurobiological alterations associated with antipsychotic medications

Whilst our understanding of the neurobiology of schizophrenia has advanced, precise mechanisms and patterns of brain pathophysiology associated with this disease remain unclear. Neuroimaging studies report evidence for several structural and functional brain abnormalities in those with schizophrenia. However, whilst some of these changes are likely related to underlying disease vulnerability or subsequent disease progression, increasing evidence suggests brain structural and functional changes observed in this disorder are partly related to antipsychotic treatment (Navari and Dazzan, 2009; Ho et al., 2011; Davis et al., 2005; Vita and de Peri, 2007). Therefore, disentangling alterations primary to the disorder from the short- and long-term effects on brain structure and function induced by treatment remains a challenge. Recognition that antipsychotics affect brain structure and function, alongside the growth of pharmacological imaging, has led to the effects of antipsychotic medications on the brain being researched in their own right (Gerretsen et al. 2009).

Studies have investigated the brains in patients with chronic schizophrenia, who, as mentioned in previous chapters, are likely to have been previously or currently treated, many for a long period. Therefore, more recent studies have investigated UHR, first episode, and antipsychotic-naïve patients, removing the confounding factor of chronic illness and treatment. A subset of studies has mapped longitudinal antipsychotic-induced alterations in brain structure or function following antipsychotic treatment. More rarely, healthy control populations have been administered single-dose antipsychotic medications. These completely remove the confound of disease-related pathophysiology, providing a 'clean' sample in which to test the effects of the antipsychotic medication. However, they naturally are limited in their generalizability to clinical populations.

Here, I outline findings from the literature regarding the neurobiological alterations associated with schizophrenia and with antipsychotic medications. I begin by briefly

reviewing structural brain changes associated with schizophrenia, followed by studies that have investigated antipsychotic-induced structural changes. Following this, I review literature regarding measures pertinent to the current study: regional cerebral blood flow (rCBF) and fMRI BOLD data, in particular relating to salience processing.

1.5.1 Brain structure

1.5.1.1 Structural brain changes in schizophrenia

One of the earliest and most robust structural brain findings reported in schizophrenia is enlarged ventricles (Johnstone et al., 1976). Numerous recent studies support findings of decreased volume of grey matter accompanied by an enlargement of the ventricles (e.g. Wright et al., 2000). Other changes implicated include decreased volume of medial temporal lobe structures, such as the hippocampus and the amygdala (Wright et al., 2000; Honea et al, 2005), and the frontal lobes, particularly the prefrontal cortex (Fornito et al. 2009).

Many of these changes were first reported in chronic schizophrenia, limiting both their generalizability and their interpretation. However, studies in FEP patients report brain changes early in the disease course, including decreased whole brain grey matter accompanied by increased ventricular volumes (Vita et al., 2006; Steen et al., 2006). Similar alterations are reported before the onset of acute psychosis in those at ultra-high risk of psychosis with prodromal symptoms (Pantelis et al., 2003).

A meta-analysis comparing chronic and FEP patients, reported decreased thalamic, amygdala, insula, and anterior cingulate cortex volumes in all patients, with more widespread cortical changes in chronic patients (Ellison-Wright et al., 2008). More recently, the prominence of structural changes in the insula, thalamus, and anterior cingulate cortex has been supported by other meta-analyses of structural changes in schizophrenia (Bora et al., 2011; Crow et al., 2013). Other meta-analyses have suggested longitudinal changes in brain structure with decreases in whole brain gray

matter, frontal gray matter, and frontal, parietal, and temporal white matter, alongside increased ventricular volumes (Olabi et al., 2011; Kempton et al., 2010). Furthermore, those at genetic high risk for schizophrenia also have altered grey matter volumes, including bigger left medial frontal gyri and smaller thalamus/putamen compared with controls (Cooper et al., 2014). These results suggest that there may be structural brain differences between the early and later stages of illness in schizophrenia, with potentially progressive cortical changes. It is possible that some of the progressive changes may be partly due to antipsychotic treatment.

1.5.1.2 Antipsychotic effects on brain structure

Studies of FEP patients, particularly those who are antipsychotic-naïve, compared with chronic patients can reveal structural changes present before treatment that may represent primary disease pathophysiology. However, such studies have produced inconsistent results (Vita and de Peri, 2007). Changes reported by some, but disconfirmed by others, include reduced whole brain volume, as well as regional reductions in frontal and temporal cortices, superior temporal gyrus, hippocampus and caudate nucleus (Vita and de Peri, 2007). Generally, results in FEP are less robust and reproducible than those in more chronic, treated cohorts, potentially suggesting progressive processes of altered structure, leading to stable and pervasive changes in chronic disease. A recent meta-analysis comparing brain structure in medicated and antipsychotic-naïve patients (Hajima et al., 2012), reported a decrease in total grey matter volume in medicated patients, associated with longer illness and higher antipsychotic dose. However, antipsychotic-naïve patients had more pronounced decreases in caudate and thalamic volumes. Nonetheless, there was less extensive grey matter loss in those naïve to treatment, again suggesting progressive changes across illness course.

Cross-sectional comparisons of treated patients with unmedicated or antipsychotic-naïve patients have shown decreased cortical grey matter in frontal and temporal

regions in patients treated with FGAs (Dazzan et al., 2005), although others have reported cortical thinning in both treated and antipsychotic-naïve patients compared with healthy controls (Narr et al., 2005). Cross-sectional comparisons of the differential effects of FGAs and SGAs on the brain suggest FGA treatment is associated with increased basal ganglia volumes and decreased cortical volumes, whereas SGA treatment is not associated with increased BG volume (Vita and de Peri, 2007; Navari and Dazzan, 2009). These differential effects of FGAs and SGAs may be evident even within the first month of treatment. Garver and colleagues (2005) found increased cortical grey matter in patients treated with SGAs that was not seen in patients treated with haloperidol for 28 days.

Longitudinal studies can investigate the timing of structural changes. Several studies investigating brain structure over a course of treatment with SGAs have reported no changes, perhaps reflecting a protective action of these drugs on brain volume (Navari and Dazzan, 2009). However, there are reports of white matter changes following SGA treatment. A recent study of 35 FEP patients, with little or no previous exposure to antipsychotic medication, reported a loss of white matter integrity in parietal and occipital regions after 12 weeks of treatment with either risperidone or aripiprazole (Szeszko et al., 2014).

Increased basal ganglia volume has been associated with both FGA and SGA treatment in some longitudinal studies (Massana et al., 2005), with higher doses associated with larger changes in volume. Whilst other studies have not found increases in this region following SGA treatment, it is possible that the conflicting results are due to dose. Risperidone prescribed in the study by Massana et al. (2005) was at a much higher dose than in other studies. At such high doses, risperidone is likely to induce particularly high D2 receptor occupancy, and an increased risk of extra-pyramidal side effects, essentially acting similarly to FGAs (Nyberg et al., 1999). Others suggest that switching from FGA to SGA treatment actually leads to decreased basal

ganglia volumes (Scheepers et al., 2001), and the action of SGAs following a switch from FGAs may be to normalise brain volumes (Navari and Dazzan, 2009).

In summary, global and regional volume changes are associated with antipsychotic treatment, but the nature of changes observed depends on antipsychotic generation. Further work is necessary to elucidate the precise patterns of change for different antipsychotic treatments, as well as to relate these to clinical changes and response to treatment.

1.5.2 Functional activation

1.5.2.1 Altered fMRI BOLD signal in schizophrenia

Functional brain activation can be measured within a variety of modalities and paradigms, both at rest or during a task. This review of the literature will concentrate on studies measuring fMRI BOLD during a task. There is much heterogeneity in tasks used, allowing fMRI to probe brain function underlying a wide variety of abilities. However, this means that observed functional abnormalities or differences between groups depend on the task context (regional abnormalities may only be detectable during a particular task), and this can limit comparability across studies.

In patients with schizophrenia, various functional activation abnormalities are reported during tasks that test motor skills, working memory, word fluency, emotional and social processing, and decision-making (Gur et al., 2010). Such abnormalities may represent failure to activate to a task. For example, studies report a lack of amygdala activation during identification of emotional expressions in patients with schizophrenia, with associated decreased accuracy (Phillips et al., 1999). Alternatively, over-activity is reported. For example, in an oddball study requiring participants to respond to targets and novel stimuli, patients exhibited increased activation in sensory and frontal areas underlying visuo-spatial processing (Gur et al., 2007). More recently, connectivity between brain regions has been a focus and studies show various abnormalities in

patients compared with healthy controls in networks across a range of experimental paradigms (Fornito et al., 2012). Together, this vast literature provides strong evidence for a broad range of functional abnormalities associated with schizophrenia.

In this project, functional activation during a salience task is investigated. Salience activation in healthy controls, and abnormalities seen in patients were outlined in chapter 1.3 (section 1.3.4, page 21) and will therefore not be repeated at length again here. Briefly, the literature provides evidence for abnormal salience processing in psychosis. Reward-related regions, including the hippocampus and anterior cingulate cortex, but particularly the ventral striatum, are repeatedly found to be under-activated during reward tasks (e.g. Smieskova et al., 2015). Additionally, failure to differentially activate reward regions for high versus low probability cues is observed. These differences are reported in FEP and chronic patients, suggesting they are stable deficits throughout the illness, and not necessarily induced by antipsychotic medications or progressive changes due to chronicity (Diaconescu et al., 2011). Furthermore, UHR patients also show abnormalities in reward and salience processing prior to onset or treatment, further supporting the existence of altered salience processing as a primary dysfunction in psychosis. Abnormal reward activation could create abnormal salience attributions to external (and internal) cues, potentially providing a mechanism by which psychotic symptoms such as delusions develop, according to the aberrant salience hypothesis (Kapur, 2003).

Hence, a range of functional abnormalities, including dysfunctional salience processing, are observed across the course of schizophrenia, within various task paradigms. Variability in results may result from differences in duration of illness and antipsychotic treatment history. At present, not enough is known about the effects of antipsychotic medications on functional activation in relevant task domains. Furthermore, it is possible that such effects may differ between those responding to treatment and those who do not. In the next section, functional changes following

antipsychotic treatment are briefly reviewed, before studies specifically exploring effects of medication on salience activation are reviewed in more detail.

1.5.2.2 Effects of antipsychotics on fMRI BOLD signal

Several reviews have collated evidence regarding antipsychotic effects on fMRI BOLD activation during a task (Davis et al., 2005; Roder et al., 2010, 2013; Liemburg et al., 2012), but there are no meta-analyses, reflecting the vast heterogeneity in methodology. Studies have implemented longitudinal, cross-sectional or mixed designs, in patients with varying degrees of previous antipsychotic exposure and disease chronicity. Tasks used include those testing working memory, motor abilities, emotional processing, verbal fluency, and other attentional or visual abilities. Several studies have also implemented reward or salience paradigms, and were discussed in depth in section 1.3.4. Table 1 provides an overview of all the studies identified and their main findings.

Studies investigating antipsychotic effects on fMRI BOLD in patients are subject to several methodological issues, such as heterogeneity of symptomatology, differences in previous antipsychotic exposure, and different stages of illness. This is problematic because it means that the baseline state of the brain is not homogenous within groups, calling into doubt whether differences between groups are due to the antipsychotic medication received or due to other illness factors. Whilst study of antipsychotic-naïve patients can solve some of these issues, such samples are challenging to recruit in large numbers. Therefore, some researchers have complemented patient studies with studies in healthy individuals, which provide opportunities to investigate antipsychotic effects independently of any underlying pathophysiological process, previous antipsychotic exposure or symptoms changes that may occur following treatment. Whilst the generalizability of these studies to the clinic is limited, they provide complementary information to patients studies, and for this reason, I also describe studies in healthy controls where relevant below.

Table 1: *Studies investigating the effects of antipsychotic medications on fMRI BOLD activation during a task*

Authors	Task	Study design	Participants (n) and medication	Main findings
a) Working memory				
Honey et al., 1999	N-back	Longitudinal	*Schizophrenia* (20): All treated with FGA at baseline; 10 remained on FGA, 10 switched to risperidone for 6 weeks *Healthy controls* (10)	Treatment with risperidone led to higher activation than continued typical treatment in frontal-parietal, supplementary motor area, and right dlPFC.
Schlösser et al., 2003	N-back	Cross-sectional	*Schizophrenia* (12): Treated with haloperidol (6) or a SGA (6) *Healthy controls* (6)	Haloperidol *versus* healthy control: increased path coefficients between left parietal and left dlPFC; right vlPFC and dlPFC; and right vlPFC and left cerebellum. SGA *versus* healthy control: increased path coefficient between thalamus and right vlPFC; left and right dlPFC; and left and right parietal cortex.
Bertolino et al., 2004	N-back	Longitudinal (with COMT/Val genotyping)	*Schizophrenia* (30): Antipsychotic free at baseline, then treated for 8 weeks with olanzapine *Healthy controls* (0)	Those with the Met allele showed improved working memory performance and prefrontal cortex physiology after treatment.
Meisenzahl et al., 2006	N-back	Longitudinal	*Schizophrenia* (12): Untreated at baseline, then treated for 12 weeks with quetiapine *Healthy controls* (12)	Treatment led to increased activation in the left vlPFC.
Surguladze et al., 2007	N-back	Cross-sectional	*Schizophrenia* (32): 16 treated with FGA depot, 16 treated with risperidone depot *Healthy controls* (8)	FGA-treated *versus* healthy controls: greater activation of mPFC in patients (failure to show task-dependent decreases). Less activation in vlPFC of patients with increased load.

Surguladze et al., 2007 *(cont'd)*				FGA-treated *versus* risperidone-treated: greater activation of mPFC in patients (failure to show task-dependent decreases). Risperidone-treated *versus* healthy controls: no significant differences.
Wolf et al., 2007	Parametric verbal working memory	Longitudinal	*Schizophrenia* (10): 8 treated with SGA at baseline, 1 treated with benperidol, 1 antipsychotic-naïve; all treated for 7–8 weeks with SGA *Healthy controls* (15)	Treatment led to changes in bilateral frontotemporal regions at increased load, including inferior frontal gyrus and superior temporal gyrus.
Schlagenhauf et al., 2008a	N-back	Longitudinal	*Schizophrenia* (10): All treated with FGA at baseline, then treated for 4 or more weeks with olanzapine *Healthy controls* (10)	In 0-back condition: increased activation in bilateral dlPFC after treatment.
Schlagenhauf et al., 2010	N-back	Longitudinal	*Schizophrenia* (11): All treated with FGA at baseline, then treated for mean 24.4 days with aripiprazole *Healthy controls* (11)	At baseline, patients showed lower activation in the dorsal ACC, activation here was not significantly different from healthy controls after treatment.
Ettinger et al., 2011	N-back (spatial)	Cross-sectional	*Schizophrenia* (45): 1 untreated, 38 treated with FGA, 6 treated with SGA *Healthy controls* (19)	FGA-treated *versus* SGA-treated: At increased load, SGA showed increased left MFG activation, FGA showed decreased activation in this same region.
Van Veelan et al., 2011	Sternberg task	Cross-sectional and longitudinal	*Schizophrenia* (23): All untreated at baseline, then treated for 10 weeks with SGA *Healthy controls* (33)	Patients showed a significantly smaller reduction in activation with practice in left dlPFC and bilateral superior parietal cortex. No significant changes following treatment.

b) Motor				
Braus et al., 1999	Finger-tap	Cross-sectional	*Schizophrenia* (13): 13 treated with FGA; 10 treated with clozapine; 3 treated with risperidone; 14 antipsychotic-naïve *Healthy controls* (15)	(ROI analysis of bilateral motor cortex and supplementary motor area). Antipsychotic-naïve *versus* healthy control: no significant differences. Antipsychotic-treated *versus* healthy control: lower supplementary motor area activation
Stephan et al., 2001	Finger-tap	Longitudinal	*Schizophrenia* (6): All antipsychotic-naïve or free at baseline, then treated for 3 weeks with olanzapine *Healthy controls* (6)	(Investigating functional connectivity in the cerebellum) Schizophrenia *versus* healthy control: higher connectivity at baseline, which normalised with treatment.
Muller et al., 2002a	Finger-tap	Cross-sectional	*Schizophrenia* (30): 10 untreated, 10 treated with haloperidol, 10 treated with olanzapine *Healthy controls* (10)	Untreated *versus* healthy control: higher activation in the motor cortex, cerebellum and basal ganglia. Haloperidol *versus* healthy control: lower activation in the basal ganglia. Olanzapine *versus* healthy control: lower activation in the motor cortex.
Muller et al., 2002b	Finger-tap	Cross-sectional	*Schizophrenia* (30): 10 untreated, 10 treated with haloperidol, 10 treated with olanzapine *Healthy controls* (10)	Untreated *versus* all other groups: higher activation in ipsilateral pallidum.
c) Emotional processing				
Fahim et al., 2005	Emotion induction	Longitudinal	*Schizophrenia* (12): All untreated at baseline, then treated for 23 weeks with quetiapine *Healthy controls* (0)	T1>T2 – right pons and bilateral midbrain T2>T1 – right dlPFC, ACC, anterior temporal pole, amygdala, and left putamen.

Stip et al., 2005	Emotional induction	Longitudinal	*Schizophrenia* (12): All untreated at baseline, then treated for mean 5.9 months with quetiapine *Healthy controls* (0)	T1>T2 – left pons and medulla oblongata. T2>T1 – right medial prefrontal gyrus and left OFG.
Blasi et al., 2009	Implicit/ explicit face matching	Longitudinal	*Schizophrenia* (12): All antipsychotic naïve or free at baseline, then treated for 8 weeks with olanzapine *Healthy controls* (12)	Schizophrenia *versus* healthy controls: patients showed greater left amygdala activation during both implicit and explicit processing. Patients showed lower activation of right vlPFC during implicit processing. Baseline *versus* follow up: Patients had reduced left amygdala activation after treatment during both implicit and explicit processing. Patients had increased right vlPFC activation after treatment during implicit processing.
Surguladze et al., 2011	Emotion induction	Cross-sectional	*Schizophrenia* (32): 16 treated with a FGA depot, 16 treated with risperidone depot *Healthy controls* (16)	Fearful faces – FGA-treated *versus* risperidone-treated: FGA showed greater activation of vmPFC, risperidone showed greater activation of the left amygdala Happy faces – FGA-treated *versus* risperidone-treated: FGA showed greater activation of the vmPFC, risperidone showed greater activation of the right cerebellum.
d) Other				
Jones et al., 2004	Verbal fluency	Cross-sectional	*Schizophrenia* (15): 7 antipsychotic-naïve, 8 treated with quetiapine *Healthy controls* (0)	Drug-naïve *versus* healthy control: healthy controls had higher activation in the left inferior frontal cortex. Drug-naïve *versus* quetiapine-treated: quetiapine treated had higher activation in the left inferior frontal cortex.

Snitz et al., 2005	Simon task (response selection)	Cross-sectional and longitudinal	*Schizophrenia* (11): All untreated at baseline, then treated with a mix of FGA and SGA for 4 weeks *Healthy controls* (16)	(ROI analysis in the dlPFC and ACC). After treatment there were no changes in the dlPFC; activation was increased in ACC.
Kumari et al., 2006	Pre-pulse inhibition	Cross-sectional	*Schizophrenia* (30): 10 treated with FGA, 10 treated with olanzapine, 10 treated with risperidone *Healthy controls* (0)	Pre-pulse inhibition elicited activation in network including insular, inferior frontal cortex and thalamus in SGA-treated but not FGA-treated patients.
Keedy et al., 2009	Visual saccades	Cross-sectional and longitudinal	*Schizophrenia* (9): All untreated at baseline, then treated with various antipsychotics for at least 4 weeks *Healthy controls* (9)	T1>T2 in bilateral intraparietal sulcus, superior temporal sulcus, vmPFC, insular regions, left dlPFC, and right ACC. T2>T1 in bilateral cerebellum, left frontal eye fields, supplementary eye field, and right ACC.
Ikuta et al., 2014	Multi-source interference task	Longitudinal	*Schizophrenia* (14): 5 antipsychotic-naïve, 9 with average 5.57 days treatment at baseline, then treated for 12 weeks with either risperidone or aripiprazole *Healthy controls* (14)	(ROI analysis in caudate, putamen, globus pallidus and thalamus). At baseline, patients had greater activation in right globus pallidus and bilateral thalamus. After treatment, activation of the right globus pallidus reduced and this was correlated with improved performance and reduced thought disturbance.

dlPFC = dorsolateral prefrontal cortex; vlPFC = ventrolateral PFC; vmPFC = ventromedial PFC; ACC = anterior cingulate cortex; OFG = orbital frontal gyrus; MFG = medial frontal gyrus; FGA = first generation antipsychotic; SGA = second generation antipsychotic; ROI = region of interest

a) Working memory

The process by which information is held in mind, manipulated, and incorporated with information stored in long-term memory is known as working memory (Baddeley and Hitch, 1974). Working memory deficits have been widely reported in schizophrenia, particularly alterations in the fronto-parietal networks underlying normal working memory performance (Royer et al., 2009; Pae et al., 2008; Glahn et al., 2005). Furthermore, worse working memory performance has been associated with altered dopaminergic signalling in the dorsolateral PFC in schizophrenia (Abi-Dargham et al., 2002). Indeed, working memory performance appears to rely on dopaminergic and serotoninergic signalling (Jakab and Goldman-Rakic, 1998), which as discussed earlier may both be disrupted in schizophrenia.

Since these neurotransmitter systems are also known primary targets of antipsychotic drugs, it is important to establish how working memory is affected by antipsychotic action. Deficits in this cognitive function are seen throughout the course of schizophrenia. Deficits in at risk mental state groups may predict psychosis onset (Pukrop et al., 2007), suggesting that working memory impairments play a role in aetiology. However, evidence suggests that antipsychotic medications do have a modulatory effect, possibly different for FGA and SGA treatments. FGA treatment is associated with lower activation in the PFC at higher cognitive loads, whilst higher activation in this region has been seen in SGA-treated patients at high cognitive load (Ettinger et al., 2011). However, some studies have reported no changes in working memory activation when patients are switched from FGA to SGA treatment (Schlagenhauf et al., 2008). Potentially, this was due to a short follow up two weeks after the switch, which may not allow enough time for activation changes to occur. However, in the same study cross-sectional comparisons with healthy individuals showed lower dorsolateral PFC activation in patients during olanzapine treatment, which was not present during previous treatment with haloperidol. This may reflect

greater neural efficiency with olanzapine. Other studies report SGA-related alterations in working memory-related activation in frontal-parietal, prefrontal, and posterior parietal regions (Honey et al., 1999; Meisenzahl et al., 2006; Wolf et al., 2007; Ettinger et al., 2011), although working memory performance is often unchanged.

Two studies, including one by our group, have studied effects of antipsychotic medications in healthy controls during working memory performance (Dodds et al., 2009; Goozee et al., 2015). In a study investigating the effects of 400mg sulpiride (a dopamine D2 receptor antagonist), neural activation following the drug did not differ to that following placebo (Dodds et al., 2009). There was also no correlation between neural activation and performance. However, activation was related to drug plasma level in the putamen, with lower drug plasma levels associated with higher neural activation when participants were required to manipulate stimuli rather than just recall them. In our study, 17 healthy men completed the n-back after placebo, haloperidol, and aripiprazole, in a randomised, blinded crossover design (Goozee et al., 2015). We found differential effects of the two drugs on working memory function. Aripiprazole worsened performance but had no effect on neural activation, whilst haloperidol did not affect performance but led to lower activation in parietal and frontal cortices, and the putamen compared with both the other conditions.

b) Motor function

Motor function deficits are widely reported in schizophrenia (Liddle et al., 1987; Dickinson et al., 2007; Morrens et al., 2007) and may underlie other cognitive dysfunctions (Salthouse, 1996). Disordered activation may accompany these performance deficits (Wenz et al., 1994; Mattay et al., 1997; Northoff et al., 1999), but the role of antipsychotic treatment in such changes is ambiguous as patients are often treated at the time they are studied. In untreated individuals with schizophrenia, Muller and colleagues (2002a/b) reported greater activation in cortical and subcortical regions compared with healthy

controls. However, others have reported no difference when comparing antipsychotic-naïve patients and healthy controls (Braus et al., 2000).

Motor tasks reliably activate cortico-striatal-thalamo-cortical loops (Alexander et al. 1990), and dopaminergic signalling is key to motor function. Considering the role of dopamine in the pathophysiology of schizophrenia and that of antipsychotic medications on this neurotransmitter system, understanding the effects of antipsychotics on motor function is important in elucidating the aetiology of such deficits, and in understanding and improving their treatment with antipsychotic drugs.

SGAs may be less likely than FGAs to induce motor deficits, with switches from a FGA to SGA associated with improved motor performance (Ahn et al., 2009; Cuesta et al., 2009; Keefe et al., 2007; Cuesta et al., 2001). Furthermore, a meta-analysis shows little effect of FGA on motor function, but improvements with SGA treatment (Woodward et al., 2005). Such differences may be expected given the differing mechanisms of action of FGA and SGA, and the association of FGA with extra-pyramidal and other motor side effects. Nonetheless, some suggest that the degree of superiority of SGAs is small, and that methodological issues, such as small sample sizes and choice of comparator dose, confound the results (Davidson et al., 2009).

Cross-sectional comparisons of FGA and SGA treatment are rarely consistent. Two related studies investigating motor activation following haloperidol or olanzapine treatment reported decreased activation compared with healthy controls in the basal ganglia following treatment with haloperidol (Muller et al., 2002a/b). However, olanzapine was associated with decreased motor cortex activation. Conversely, another study found FGA but not SGA treatment led to lower activation in cortical regions (Braus et al., 1999). Longitudinal studies suggest treatment with olanzapine normalises baseline differences between healthy controls and patients, for example reversing lower activation in the sensorimotor cortex after eight weeks of treatment (Bertolino et al., 2004). As such, whilst the literature supports the modulation of motor performance and activation deficits in

schizophrenia by antipsychotic medications, the precise pattern of changes and effects of different antipsychotic medications remain to be elucidated.

Studies of motor performance in healthy individuals suggest impaired motor performance following SGA administration (Beuzen et al., 1999; Wezenberg et al., 2007; de Bruijn et al., 2006; Morrens et al., 2007). The FGA haloperidol appears not to affect performance in healthy controls, but does appear to lead to decreased motor activation in several motor regions, including the supplementary motor area, primary somatosensory cortex, premotor cortex, putamen, thalamus and cerebellum (Tost et al., 2006). However, in a study carried out by our group, *greater* activation in temporal, parietal, and frontal regions was seen following haloperidol, than after either placebo or aripiprazole. The only region of reduced activation was in the right caudate. Neural activation following aripiprazole did not differ from that following placebo. These differences may be accounted for by the differences in task used or by sample size. Our study was larger, and so whilst lower activation was seen in a few participants, increased activation may be more common but may go undetected in a smaller sample. Regardless, with so few studies it is difficult to draw more certain conclusions.

c) Emotional processing

Individuals diagnosed with psychotic illnesses often have associated impairments in social functioning, which may relate to other cognitive and emotional deficits, such as blunted affect (Kirkpatrick et al., 2001), facial emotional processing deficits (Tsoi et al., 2008), reduced facial expression during social interactions (Mattes et al., 1995), and abnormalities in emotional perception (Edwards et al., 2001).

Several studies report abnormal activation patterns to emotion stimuli in schizophrenia, although results depend on the precise tasks used, as well as whether patients are treated or not at the time of study. Dysfunctions in emotion perception and expression have been related to abnormal amygdala activity in schizophrenia (Blasi et al., 2009). A meta-analysis has suggested the presence of activation abnormalities across a range of

regions during emotional processing, including less extensive activation of bilateral amygdala, parahippocampal gyrus and fusiform gyrus, right superior frontal gyrus, and lentiform nucleus in patients with schizophrenia compared with healthy controls (Li et al., 2010). Furthermore, during the task patients activated the left insula whilst controls did not.

As emotional deficits, such as blunted affect, are difficult to treat and may relate to poorer functional outcomes (Stip et al., 2005), it is important to understand how they are modulated by antipsychotic treatment. Comparing emotion induction in 16 patients treated with FGA depot (a mixture, including haloperidol decanoate and flupentixol decanoate) with 16 patients treated with SGA depot (risperidone long-acting injection), activation was related to the type of treatment received (Surguladze et al., 2011). For example, during presentation of fearful faces, FGA-treated patients had higher activation of ventromedial PFC than SGA-treated patients. However, SGA-treated patients showed greater activation of the left amygdala than the other patient group. Longitudinal studies of emotion induction report decreased activation in subcortical regions of the midbrain, and increases in cortical, particularly frontal, regions, such as the dorsolateral PFC, anterior cingulate, and orbital frontal gyrus following five months treatment with quetiapine (Fahim et al., 2005; Stip et al., 2005). Another study reported decreased amygdala activation (making patients more like healthy controls) following 8 weeks of olanzapine treatment in patients with schizophrenia (Blasi et al., 2009). FGAs and SGAs likely have differential effects. Thus, whilst antipsychotics likely modulate emotion processing in subcortical and cortical regions, the effects seen may depend on the antipsychotic type. Furthermore, some results are inconsistent and the precise patterns of change are yet to be elucidated.

d) Other tasks

The effects of antipsychotics on several other tasks have been investigated in schizophrenia. Some show a normalizing effect of SGA treatment, for example on

verbal fluency (Jones et al., 2004) and attentional control tasks (Ikuta et al., 2014), making patients more like healthy controls. Many longitudinal studies report changes in frontal regions following antipsychotic treatment. For example, increased anterior cingulate cortex activation was seen following 4 weeks of treatment with FGA and SGAs during a response-selection task (Snitz et al., 2005). Similarly, activation during visual saccades following four weeks of antipsychotic treatment with risperidone, ziprasidone or haloperidol was increased in ventromedial PFC, insular regions, left dorsolateral PFC, and right anterior cingulate cortex, whilst decreases were seen in bilateral cerebellum, left frontal eye fields, and supplementary eye fields (Keedy et al., 2009). In a study of pre-pulse inhibition, the effects of different treatments (FGA versus risperidone) were investigated (Kumari et al., 2002), reporting that activation in a network of insular, inferior frontal, and thalamic regions was activated during the task in SGA-treated and not FGA-treated patients.

These studies use widely varying methodologies and tasks, making it difficult to integrate their results. However, together the literature suggests that antipsychotic medications modulate various cognitive functions and their underlying neural activation patterns and that these alterations differ depending on the antipsychotic administered.

1.5.2.3 Effects of antipsychotics on measures of salience

Given the potential role of salience in the development of core symptoms of schizophrenia (delusions and hallucinations), investigating the effects of antipsychotics on these processes is incredibly important. Studying whether measures of salience are affected by antipsychotic medications, whether patients more closely resemble healthy controls after treatment, and whether these changes are related to changes in psychotic symptoms, provides a test of the importance of aberrant salience in the pathology of the disorder. Very few previous studies (Table 2) have investigated the effects of antipsychotics on salience in this way, and most of those that have, used reward tasks rather than tasks providing measures of salience attribution (as in the

SAT). Only one recent task has used the SAT to conduct cross-sectional analyses of the effects of treatment on measures of salience (Smieskova et al., 2015).

Table 2: *Studies investigating the effects of antipsychotic medications on reward and salience activation*

Authors	Task	Study design	Participants (n) and medication	Main findings
Juckel et al., 2006	MID	Cross-sectional	*Schizophrenia* (20): 10 FGA-treated; 10 SGA-treated. *Healthy controls* (10)	(ROI analysis in the bilateral ventral striatum). Healthy controls showed increased activation to reward anticipation. SGA-treated showed increased activation in left ventral striatum only. FGA-treated failed to show any increase in activation.
Kirsch et al., 2007	Reward conditioning	Cross-sectional	*Schizophrenia* (30): 13 FGA-treated or a mix of FGA and SGA; 17 SGA-treated. *Healthy controls* (0)	(ROI analysis in the bilateral ventral striatum). Patients treated only with SGA showed higher right ventral striatal activation to reward anticipation than other patients.
Schlagenhauf et al., 2008b	MID	Cross-sectional and longitudinal	*Schizophrenia* (10): FGA-treated at baseline and then switched to olanzapine for at least 4 weeks. *Healthy controls* (10)	Healthy controls had higher ventral striatal activation during reward anticipation than patients when FGA-treated at baseline. After olanzapine treatment, patients showed a significant activation of the ventral striatum and did not differ from healthy controls.
Nielsen et al., 2012	MID	Longitudinal	*Schizophrenia* (23): Antipsychotic-naïve at baseline, then treated for at least 6 weeks with amisulpride. *Healthy controls* (24)	At baseline, patients had lower activation in the ventral striatum during reward anticipation. After amisulpride treatment, patients had increased activation in the ventral striatum and no longer differed from healthy controls. Increased activation in ventral striatum was positively correlated with improvements in positive symptoms.

Smieskova et al., 2015	SAT	Cross-sectional	*Schizophrenia* (29): 17 unmedicated FEP; 12 SGA-treated (plus 34 with at risk mental state). *Healthy controls* (19)	Compared with healthy controls, unmedicated patients had lower activation during adaptive salience in the left dorsal cingulate gyrus. Compared with healthy controls, medicated patients had lower activation during adaptive salience in the right insula. In unmedicated patients, the severity of hallucinations and delusions was negatively correlated with activation in the insula and anterior cingulate cortex during adaptive salience.

MID = monetary incentive delay; ROI = region of interest; FGA = first generation antipsychotic; SGA = second generation antipsychotic

Five studies have investigated reward or salience processing in schizophrenia within a pharmacological imaging paradigm. Most were cross-sectional comparisons (Juckel et al., 2006b; Kirsch et al., 2007; Schlagenhauf et al., 2008b; Smieskova et al., 2015) and only one was longitudinal (Nielsen et al., 2012). Two further studies investigated the effects of antipsychotic administration on reward in healthy individuals without psychosis (Abler et al., 2007; Bernacer et al., 2013).

The ventral striatum is a key area to reward and salience processing. Both healthy controls and SGA-treated patients exhibit activation here to reward-indicating cues during the MID task (Juckel et al., 2006b). However, in the same study, FGA-treated patients failed to activate the ventral striatum under the same conditions, and this was associated with negative symptoms. Similarly, ventral striatal activation in patients became more similar to that of heathy controls following a switch from FGA to SGA (olanzapine) (Schlagenhauf et al., 2008b). Furthermore, in a simple conditioning task in patients with schizophrenia (treated with either FGA only, a mixture of FGA and SGA or SGA only) cross-sectional region of interest analyses in the bilateral ventral striatum revealed greater activation during reward anticipation in patients treated with SGA only compared with the other patient groups (Kirsch et al., 2007). In the only study to use the SAT to measure salience, medicated and unmedicated patients with FEP differed from healthy controls in different brain regions (Smieskova et al., 2015). Unmedicated patients had lower activation during adaptive salience in the left dorsal cingulate gyrus, whereas in medicated patients lower activation associated with adaptive salience in the right insula was observed. There were no differences seen in activation during aberrant salience processing.

The only study to investigate the longitudinal effects of antipsychotic medication on reward processes studied 23 antipsychotic-naïve patients with schizophrenia and 24 healthy individuals completing the MID (Nielsen et al., 2012). Patients were scanned twice; at baseline and then following six weeks or a period of 2 weeks at a stable dose

of amisulpride. Before treatment, abnormal reward activation was seen, with lower activation in patients than healthy controls in the bilateral ventral striatum. At follow up, patients had an increased level of activation in this same region, and were no longer significantly different from healthy individuals, suggesting that the antipsychotic medication had acted to normalise reward activation. Furthermore, increased activation in the ventral striatum was positively correlated with improvements in positive symptoms, consistent with the idea that normalisation of reward-related activation was associated with a reduction in psychotic symptoms.

Two studies investigated the effects of antipsychotics on reward and salience in healthy controls (Abler et al., 2007; Bernacer et al., 2013). Bernacer and colleagues (2013) investigated the effects of methamphetamine on reward-related processing in the ventral striatum and ventromedial PFC. They found that psychotic symptoms induced by this drug correlated significantly with altered activation in the ventromedial PFC, and these effects were not modulated by pre-treatment with the antipsychotic amisulpride.

In a double-blind study using a crossover design to investigate fMRI BOLD during a delayed incentive task, eight healthy controls were compared after placebo and single-dose olanzapine (Abler et al., 2007). The authors reported reduced activation in the ventral striatum, anterior cingulate cortex, and inferior frontal regions after olanzapine. There were also slowed reaction times to cues more highly predictive of reward. The analysis showed that whilst reductions in some regions appeared to be due to an overall drug effect, the results in the ventral striatum were specific to the attribution of salience, as the reduction represented a loss of differential activation to high versus low probability of reward rather than a general reduction. It is possible that different effects are seen in patients and healthy controls because drugs act on a different neural substrate, i.e. normal functioning activation in healthy controls. Possibly a U-shaped curve of optimal functioning may underlie incentive salience processing. Thus, in healthy controls, functioning of the ventral striatum is optimal for incentive salience

processing, but treatment with an atypical antipsychotic alters this functioning to beyond the optimal range. In patients, ventral striatal activation is decreased and thus suboptimal for salience processing. In such a case, atypical antipsychotic treatment alters functioning such that it is within the optimal range by increasing the activation in this region.

There are limited studies of antipsychotic effects on salience and reward-related activation in schizophrenia. The few studies undertaken suggest an important role of the ventral striatum, in which dysfunctional activation may be improved with SGA, but not necessarily with FGA treatment. The current study provides a further opportunity to replicate these results, using a powerful longitudinal design, in a group of minimally-treated first episode psychosis patients. Furthermore, it is the first to use such a design to investigate the effects of antipsychotics on activation during the SAT, a task that provides explicit and implicit measures of aberrant and adaptive salience.

1.5.3 Brain perfusion

Functional neuroimaging attempts to measure neuronal activation. However, the BOLD response actually comprises several parameters, including cerebral blood volume (CBV), blood oxygenation ($CMRO_2$), and cerebral blood flow (CBF), and provides only a proxy of neuronal activation. This complicates the interpretation of results somewhat. However, perfusion imaging methods, such as arterial spin labelling (ASL), allow just one of these parameters, CBF, to be investigated. This removes the influence of other parameters, such as CBV and $CMRO_2$, and provides a quantitative measure of brain activity in ml blood per 100mg of tissue per minute.

CBF is the blood flow through a volume of tissue in a set period of time. It is visualised using either an exogenous tracer (as in bolus-tracking) or an endogenous tracer (as in ASL). Early functional neuroimaging studies used bolus-tracking methods, injecting compounds such as Gadolinium into the blood stream. These compounds alter the local magnetic susceptibility of blood, and this can be detected by a signal change, and

thus tracked as the bolus moves through the cerebral vasculature. ASL allows quantitative measurement of CBF using magnetically labelled arterial blood water as an endogenous tracer (Detre et al. 1992). Therefore, this technique does not require any injected compounds, meaning it is non-invasive and repeatable. This is particularly useful in psychopharmacological paradigms in which several images can provide a time course of changes across treatment (see Methods, page 131, for more details).

Cerebral blood flow can be measured during a task or at rest (resting cerebral blood flow, rCBF), the latter of which provides a measure of basal brain activity. Importantly, rCBF appears to correlate with other measures of brain function. It is closely correlated with neuronal metabolic measures (Raichle, 1976), and ASL techniques reveal correlations between rCBF and regional brain activity measured using other techniques (Uludag et al., 2004).

There is mounting evidence that antipsychotic medications alter rCBF, with reports that this may be linked to symptom amelioration (Pinkham et al., 2011). Regions that have been linked to psychosis elsewhere in the literature are often found to show altered patterns of rCBF in studies investigating antipsychotic effects (Miller et al., 2001; Lahti et al., 2003). Studies in patients have investigated chronic use across weeks, months, or longer but studies in healthy controls suggest that rCBF may be sensitive even to early antipsychotic action. Indeed, effects have been identified after single-dose administration, and what is more, these changes may be specific to antipsychotic type (Handley et al., 2013). Understanding these changes can aid interpretation of other brain changes, such as structural alterations, by providing the physiological mechanisms by which these may occur (Scheepers et al., 2001).

I have published a systematic review and meta-analysis of the literature (Goozee et al., 2014, Appendix A), which collates previous findings regarding the effects of antipsychotics on CBF and any relationships with treatment response. This paper concluded that antipsychotics appear to have an effect on rCBF, which differs

depending on antipsychotic generation. FGAs tend to have subcortical effects, while SGAs more often lead to alterations in cortical regions. The review and a small, exploratory meta-analysis implicated rCBF in the frontal cortex and basal ganglia as particularly affected by antipsychotic treatment. However, in the review I also noted that few studies use a priori definitions of treatment response, which makes it difficult to predict outcomes to antipsychotic treatment using measures of rCBF. There was also a high level of heterogeneity between studies in terms of patient samples, methods, and treatment administered. These considerations helped to inform the use of cASL in the current study, to investigate the potential for rCBF to predict symptomatic improvement.

Given the literature outlined above, rCBF is a good candidate biomarker for antipsychotic treatment effects and treatment response. I therefore use ASL in the current study, to investigate the effects of antipsychotic medication on rCBF at rest in our sample of FEP patients.

1.5.4 Chapter summary and conclusions

A wide range of neurobiological measures have been investigated to try to understand how antipsychotic treatment affects the brain. Neurobiological alterations have been observed in schizophrenia using various techniques, showing structural and functional differences compared with healthy controls. The research reviewed in this chapter suggests that some of these changes may be due to treatment. Indeed, antipsychotic medications can alter both brain structure and function, and differential effects are often seen for different antipsychotics. Whilst FGA and SGA broadly affect these parameters in different ways, it might even be possible to differentiate the effects of specific types of antipsychotic within these categories, with the mechanisms of action and receptor affinities determining the changes seen.

Such studies allow us to see the ways in which the brain changes under treatment. Moreover, such findings provide a basis from which brain measures might potentially allow prediction of treatment response. Understanding the differences in the effects of

antipsychotics on the brains of patients who respond to antipsychotic medications and those who do not, can provide insight into the precise mechanisms of effective treatment. Furthermore, baseline brain measures may be used for prediction of later response. Together, these findings can help us to better understand current treatments and how they work, identify potential new treatment targets (particularly for those who do not respond to treatments currently in use), and they could guide treatment, allowing a more personalised approach to prescribing.

1.6 Prediction of antipsychotic treatment response

Antipsychotic medications are the first choice of treatment for psychosis and at a group level, antipsychotics exhibit efficacy compared with placebo for treating the symptoms of psychosis (Leucht et al., 2013). However, at the individual level, response to treatment is variable. As many as 40% of patients do not respond to the first antipsychotic (Barnes, 2011), and it is not currently possible to predict later response at first presentation in clinical services. Therefore, treatment is carried out in a "trial and error" manner, with no objective ways to predict whether a particular patient will respond or not (Piquette-Miller and Grant, 2007). Furthermore, given current reliance on relatively subjective clinical assessments, both diagnostic accuracy and treatment plans for patients with schizophrenia are likely influenced by cultural and value judgements (Fulford et al., 2005). Whilst antipsychotics have been compared to identify which should be trialled first (Johnsen et al., 2010), this approach only accounts for effectiveness at a group-level, and does not consider that different individuals may benefit from different antipsychotics.

Approaching antipsychotic treatment in this way can be problematic for several reasons. Inevitably, a proportion of patients will remain treatment resistant or partially responsive, with residual symptoms and distress associated with poorly managed psychotic symptoms. Prolonged distress may have a greater impact on function as they trial several antipsychotic medications before finding a treatment that works for them. Additionally, this costs services extra time and money; treating residual symptoms and also dealing with associated morbidity, mortality, and adverse drug reactions or side effects (Piquette-Miller and Grant, 2007). Furthermore, this approach stunts development of new treatments. Elucidating the biological variation underlying treatment resistance and poor response may improve treatment for patients, reduce costs for services, and provide potential new treatment targets.

Understanding neurobiological heterogeneity in response to treatment in schizophrenia could provide objective predictive biomarkers. If heterogeneity in treatment response

reflects differences in aetiology, then understanding differences in individual biological factors underlying variability may provide the basis for developing predictive 'tools'. This could inform aetiological mechanisms, as well as diagnostics and therapeutics, supporting improved treatment management, patient stratification, and personalised treatment planning (Gerretsen et al., 2009).

Several factors have been associated with outcome in schizophrenia, and research to identify prognostic predictors has explored clinical, psychosocial, and biological factors with some success. However, many studies still consider these predictive relationships at a group-level, providing only general (rather than individual) knowledge about what kinds of patients are likely to benefit from particular treatments. In contrast, recent development of machine-learning techniques holds promise for individual-level prediction, which could therefore allow truly personalised investigations of likely treatment outcome (Mourao-Miranda et al. 2012).

This chapter outlines clinical and biological factors that have been associated with treatment outcome or used as prognostic predictors. Clinical, genomic, and proteomic research will be mentioned only briefly, allowing space for a full discussion of neuroimaging biomarkers of treatment response. However, first, I will discuss the concept of remission in schizophrenia, as this is central to the assessment of response to treatment, the focus of this thesis.

1.6.1 Expectations for prognosis and outcome in schizophrenia

For much of its history, schizophrenia has been identified as a progressive, deteriorative or serially relapsing disease (Levine et al., 2011). According to this view, sufferers could expect little, if any, recovery of social relations and occupational function, or even resolution of symptoms. Such a diagnosis was deemed a 'life sentence'; a chronic illness usually to be managed within the asylum system.

The introduction of pharmacological treatments and community care, as well as long-term prospective studies of illness course, have altered this state of affairs. Greater optimism and hope for recovery (a previously neglected concept in schizophrenia) were fostered by results showing heterogeneity in outcome of the disorder (e.g. Liberman et al., 2002; Morgan et al., 2014). Certainly, some patients develop chronic illness. However, many recover, enjoy long periods of remission, and learn to adapt to their illness, recovering much of their previous functional capacity. Furthermore, early identification and treatment aims to curtail much of the disruption associated with uncontrolled symptoms. Possibly, the change from asylum-centric care to community-based case management did not simply result from availability of new pharmacologic treatments but also reflected (and encouraged) a change in attitude towards the possibility of recovery.

1.6.2 Recovery in schizophrenia

Definitions of recovery, and the related concept of remission, differ depending on the perspective taken. Patients, clinicians, and researchers may approach the subject with their own priorities, although their definitions will probably overlap to some degree.

Whilst clinicians and researchers are likely to focus on symptoms, patients' personal definitions are likely to be broader and more idiosyncratic. Reviews of studies looking at personal definitions of recovery find various commonalities or themes across individual definitions. Leamy and colleagues (2011) identified five recovery processes in personal accounts of recovery. These include connectedness, hope and optimism, identity, meaning in life, and empowerment. However, in black and ethnic minority samples, spirituality and stigma appear more important.

The focus for recovery clinically often tends to be on the remission of symptoms. Clinical definitions of remission and recovery are important to be able to determine suitable treatments, manage treatments according to need, and identify unmet need. They are

likely to include symptom reduction, relapse prevention, avoidance of hospital admittance, and return to work.

Within psychiatric research the definition of recovery tends to differ from these other two perspectives. A definition or operationalization of remission and recovery for research needs to be quantifiable, standardized to be applicable across a range of study contexts, valid, reliable, and generalizable. To investigate treatment response, there needs to be a treatment goal, which is standardised and appropriate for use by different researchers or in different studies and samples, to allow comparisons of treatments. Within research, definitions of recovery and response are often reached by consensus to enable the efficacy of treatments to be determined, and to compare outcomes or treatments. Consensus criteria for remission in schizophrenia are outlined and discussed below (Andreasen et al., 2005).

Of course, an important aspect of translational research is ensuring that operationalizations of treatment response are clinically relevant, and relate to personal priorities of patients, i.e. they should indicate improved functioning and not just symptom reduction unrelated to other relevant outcomes. However, remission can be seen as a necessary although insufficient step towards recovery, which is a longer-term state that encompasses improvements in social and occupational function, quality of life, and the like (Andreasen et al., 2005). Therefore, it is an appropriate treatment goal for research.

1.6.3 Consensus definition for research

Until recently, a lack of standardised remission criteria was a problem for research into outcomes in schizophrenia. It limited the ability to compare findings across studies using different criteria and it made findings difficult to interpret as it could be unclear what the remission criteria meant clinically. In 2005, the Remission in Schizophrenia Working Group developed specified criteria to overcome this (Andreasen et al., 2005). Subsequently, these criteria have been applied in numerous settings and in many studies. In addition, they have been shown to relate to social and occupational

functioning, with patients defined as ‘remitted’ doing better in other functional domains than those defined as ‘non-remitted’ (Emsley, 2011). These standardised criteria address a number of problems that were previously encountered in research that aimed to assess response to treatment.

Prior to the consensus criteria, early studies tended to use general descriptive criteria, such as ‘mild illness’ versus ‘active psychosis’. However, the judgement of the category to which an individual should be assigned was not objective, and may have differed between different studies or even different raters within a study.

Definitions of remission that were subsequently developed for research focused on the reduction of (usually positive) symptoms. This accompanied the development of assessments such as the Scale for Assessment of Positive Symptoms (SAPS), the Scale for Assessment of Negative Symptoms (SANS), and the Positive and Negative Syndrome Scale for Schizophrenia (PANSS). There are two main approaches to using symptom scores to assess response to treatment. Firstly, change scores may be used to indicate the level to which a treatment has reduced (or otherwise) a symptom score. This method has the benefit of providing a continuous measure of treatment response, and can be used where the groups of treatment responders or non-responders suffer from a small sample size. However, a limitation with this approach is the variability in baseline scores, as well as how to define the extent of change needed for a *clinically significant* change. Is it possible for two individuals to have a decrease in PANSS score of the same magnitude, but to differ vastly in the severity of their illness following this change if one individual was much more ill to begin with than the other. Therefore, the second alternative approach that has been proposed is to use threshold levels of illness severity, below which remission is ‘achieved’ (Leucht et al., 2006). This is the procedure used in applying the Andreasen remission criteria.

Within the Andreasen remission criteria, eight PANSS items are used to define remission: delusions (P1), conceptual disorganisation (P2), hallucinations (P3), blunted

affect (N1), passive/apathetic social withdrawal (N4), lack of spontaneity and flow of conversation (N6), mannerisms and posturing (G5), and unusual thought content (G9). Remission is achieved with a score of three or less ('mildly present and does not interfere with daily life functioning') on all eight items. Importantly, these criteria have been shown to relate to several broader clinical outcomes, such as quality of life, occupational function, social function, and subjective wellbeing (Helldin et al., 2007; Emsley et al., 2007; Nasrallah and Lasser, 2006). The consensus group also considered the long term and potentially relapsing course schizophrenia can take, and so suggested that remission was achieved when these items remained mild or less for six months. In this study, we did not use the six months criteria, as patients were medicated for 4 weeks, a period during which it is suggested most response to antipsychotic treatment occurs (Kinon et al., 2010). Furthermore, response at 4 weeks has been shown to reliably predict later response up to 12 months (Leucht et al., 2007; Kinon et al., 2010).

In this thesis, both change scores on the PANSS and the Andreasen remission criteria are used to assess treatment response. Thus, remission of symptoms according to the Andreasen criteria constitutes a 'responder'. Meanwhile, failure of symptoms to remit constitutes a 'non-responder'. Using this categorisation of patients, we can compare responders and non-responders in a number of ways to try to determine the neurobiological basis of treatment response (and non-response). The aim is therefore to use various biological parameters to predict to which category a patient will belong (responder or non-responder). However, due to relatively small numbers of non-responders, we also use percent change scores to provide a continuous measure of treatment response, where categorical comparisons may be underpowered. Continuous variables will allow prediction of response to treatment, by exploring relationships between neurobiological factors and the *degree* of response to treatment.

A vast number of potential clinical and biological predictors of treatment response, including genetic, proteomic, and neuroimaging, have been investigated. Predicting response to treatment using neuroimaging is a recently emerging field in psychiatry, and

is the approach chosen in the current project. In the next section, I will outline the evidence for predictive biomarkers of treatment response in psychosis, concentrating primarily on neuroimaging.

1.6.4 Factors predicting response to treatment

The observation that not all patients respond well to antipsychotic medications naturally leads to the question of why this might be. Understanding the factors that determine response to treatment could be beneficial in a number of ways, not least because it might allow prediction of treatment response. Furthermore, the ability to determine who will respond to a treatment, and who will not, *before treatment commences* is vital if the aims of personalised medicine in psychiatry are to be met.

It is worth bearing in mind that two broad categories of studies exist that attempt to predict outcomes. Some studies use clinical and biological predictors for prognosis to predict longer term, broader outcomes that relate to general functioning. Others use a narrower, more specific concept of treatment response, such as symptom reductions or the Andreasen remission criteria, as I have outlined above.

1.6.4.1 Clinical predictors of treatment response

Demographic and clinical factors were the first to be investigated as potential predictors of antipsychotic treatment response. A review suggests that insight, early treatment response, and duration of untreated psychosis (DUP) may all be particularly important for outcomes in psychosis (Emsley et al., 2008). These factors might mediate outcome via numerous pathways, for example determining compliance with treatment, engagement with services or other non-specific factors.

Where relationships between clinical factors and antipsychotic response have been explored, a good response has been associated with good premorbid adjustment and shorter DUP (Schennach et al., 2012). Whilst many studies have identified an early good response to treatment as predictive of subsequent good response (e.g. Levine

and Leucht, 2012; Giegling et al., 2012; Ruberg et al., 2011), it is possible that this prediction is only reliable in the short-term, and does not hold for longer-term outcomes (Schennach et al., 2012).

A common characteristic of clinical predictors is that they deal with group-level prediction. On the whole, patients with a longer DUP tend to do worse than those with a shorter DUP. However, if we are faced with a patient in the clinic, and asses their DUP, we cannot use this measure to predict reliably how well this particular individual will fare following treatment or in response to a particular antipsychotic medication. There is no precise relationship between a certain cut off length of DUP and good or poor treatment response. Clinical factors tend to be imprecise, allowing only probabilistic statements about risk of a good or poor response. Neurobiological factors in combination with machine learning methods hold the promise of more precise, individualised prediction.

1.6.4.2 Biomarkers of treatment response

The term biomarker is used across health and medical disciplines, and it has been defined in a number of ways. Strimbu and Tavel (2010) define biomarkers as follows:

> *"The term "biomarker" … refers to a broad subcategory of medical signs – that is, objective indications of medical state observed from outside the patient – which can be measured accurately and reproducibly. Medical signs stand in contrast to medical symptoms, which are limited to those indications of health or illness perceived by patients themselves."*

The authors stress the difference between biomarkers and clinical endpoints. The latter are the aim of treatment, incorporating the subjective sense of wellbeing and symptom experience of the patient. Biomarkers on the other hand do not necessarily correspond to the clinical state of the patient, but are often surrogate endpoints whereby they reliably and accurately predict a clinical endpoint. Another earlier definition from the

National Institutes of Health Biomarkers Definitions Working Group (2001) defined a biomarker as:

> *"A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention."*

These definitions suggest that a substance, structure, or process that can be objectively measured in the body to predict disease or outcome of treatment can be classed as a biomarker. Therefore, any medical signs, from pulse and blood pressure, through gene and blood factors, to brain volumes or activations may be used as predictive biomarkers if they can be shown to reliably and accurately predict treatment outcomes.

References to biomarkers do not always relate to the prediction of treatment response. In a review, Prata and colleagues (2014) collate examples of biomarkers that can be defined as 'predictive', 'prognostic', 'monitoring', and 'diagnostic'. Predictive biomarkers are particularly useful in the current context. Predictive biomarkers are biological variables that "predict a response to a specific therapy, be it psychological or pharmacological, to help determine the optimal treatment in a stratified or personalized manner before it is commenced". In the current project, I investigate potential predictive imaging biomarkers with the broader view to informing a personalized approach to antipsychotic treatment.

Within psychiatry, there are currently no objective diagnostic or prognostic biological tests. However, several genetic, proteomic, and neurobiological markers are being actively researched.

1.6.4.3 Genomic and proteomic predictors of antipsychotic treatment response

The role of genes in schizophrenia has been extensively researched, and genetic factors have emerged as important not only in the development of psychosis, but also in the variability of response to treatment (Reynolds, 2012). Studies of monozygotic twins suggest a genetic influence on response to treatment, with monozygotic twins showing strong concordance in response to clozapine (Vojvoda et al., 1996) and olanzapine (Mata et al., 2001). Most genetic studies have used candidate gene approaches, which are hypothesis-driven investigations of genes for proteins that are either known, or thought, to play a role in the drug action. Thus, genes involved in both the dopamine and serotonin systems have been widely researched. For example, the DRD2 gene, coding for the dopamine D2 receptor, has been shown to relate to response to haloperidol (Schafer et al., 2001). Similarly, polymorphisms at genes encoding serotonin receptors have been related to antipsychotic treatment response, and may be more important in the remission of negative than positive symptoms (Reynolds et al., 2005/2006).

Genetic studies are subject to many of the same criticisms as neuroimaging studies of the effects of antipsychotics on the brain. They suffer from small sample sizes, and heterogeneity in patients' diagnoses and drug histories (Nnadi and Malhotra, 2007). However, in drug-naïve patients, polymorphisms at a promoter region of the DRD2 gene have been related to speed of response to SGAs (Lencz et al., 2006).

Proteomic alterations are also reported in schizophrenia, and provide another source of potential biomarkers to predict treatment response to antipsychotic medications (Guest et al., 2013). Some promising findings are reported, despite challenges to proteomic analyses (including the inaccessibility of the live human brain for proteomic interrogation, the potential inability to detect central changes in the periphery, etc.; Martins-de-Souza et al., 2012). Analysis of serum prolactin levels show a relationship between higher levels and better outcomes following five years of treatment

(Shrivastav et al., 2012). Furthermore, several proteins important in inflammatory and hormonal pathways have been shown to predict improvements in positive (e.g. IL-16, C-reactive protein, and prolactin) and negative (e.g. insulin) symptoms (Schwarz et al., 2012).

The hope for proteomic analyses is that they will reveal molecular tests to identify responders to specific medications. As such, personalised medicine approaches could be developed based on simple laboratory tests, for example blood samples, to determine which antipsychotic medication a patient is likely to benefit from. However, it has been suggested that different levels of biological analyses must be integrated, not only genetic and proteomic, but also transcriptomic and metabolic, to develop a systems biology approach that will better equip clinicians and researchers to predict treatment response outcomes in patients (Guest et al., 2013).

1.6.4.4 Imaging predictors of antipsychotic treatment response

Neuroimaging is emerging as a promising source of biomarkers of antipsychotic treatment response, with potential for clinical translation (Dazzan et al., 2015). Whilst genetics and proteomic biomarkers have the benefits of objectivity, low cost, and reliability, they also suffer from small effect sizes and low prevalence, limiting their clinical application (Prata et al., 2014). Brain imaging has been shown to have larger effect sizes with replicable results (although this is largely as diagnostic biomarkers). Coupled with machine-learning approaches, imaging offers the potential of an automated, accurate tool with which treatment response could be predicted. However, whilst recent research efforts have revealed associations between various brain measures and response to treatment, it remains to be clarified which measures are of greatest predictive value, and thus have value in clinical management.

To identify biomarkers with a high predictive accuracy and generalizability requires large scale, multisite studies (Kempton and McGuire, 2014). Larger sample sizes would ensure studies are adequately powered, and would also enable analyses of subgroups

within the heterogeneous umbrella of schizophrenia. Furthermore, studies across multiple sites can increase the generalizability of results, whilst ensuring standardized procedures are used at all sites. However, it has often been difficult to pool data from different studies, as both samples and methods are greatly heterogeneous.

1.6.4.4.1 Structural imaging predictors of treatment response

Structural biomarkers have been widely researched for many years, and whilst a greater degree of structural abnormality has been associated with a broadly worse outcome, no clear associations have been shown with response to treatment (Lawrie et al., 2011).

An early review and meta-analysis found a lack of significant association between brain structure and treatment response (Friedman et al., 1992). However, the authors highlighted the influence of heterogeneity in samples and methods from different studies, suggesting the need for greater standardization. More recent studies have combined structural measures with clinical variables, for example reporting that a greater degree of baseline psychopathology predicts a better response to treatment, but that patients with enlarged ventricles are more variable in both symptomatology and response to treatment (Mauri et al., 1994). A recent review by Dazzan and colleagues (2015) collated results from studies that investigated the relationship between structural MRI parameters and outcome in FEP, finding alterations in medial temporal and prefrontal cortical areas to be promising neuroanatomical markers of poor response to treatment.

Often studies investigate specific brain regions in relation to treatment response with variable results. For example, some have reported a relationship between larger hippocampal volumes and a good response to risperidone (Savas et al., 2002), but others have failed to find any relationship with olanzapine treatment (Molina et al., 2003a). The prefrontal cortex has also been investigated, particularly in relation to clozapine response. An early study reported no relationship between improvements on

the BPRS and frontal or prefrontal volumes in treatment-resistant patients with schizophrenia switched from typical antipsychotics to clozapine (Lauriello et al., 1998). However, Molina and colleagues (2003b) studied 25 treatment-resistant patients with schizophrenia following clozapine treatment and reported that greater improvements in negative symptoms were related to increased volume of the prefrontal cortex, whilst the best predictor of improvement of positive symptoms was temporal volume.

Early studies are subject to methodological limitations, such as heterogeneous samples, with many participants having previous exposure to antipsychotic medication. Given the evidence that antipsychotic medication alters brain structure (refer back to chapter 1.5), the baseline scan in such patients is likely affected by their previous treatment. Furthermore, chronicity and duration of illness may be a further consideration, as neurodegeneration or progressive pathological processes may introduce further variance and confounding factors into the sample. As elsewhere, these complications are avoided by implementing studies in antipsychotic-naïve or minimally treated patients experiencing their first episode of psychosis.

An early study of 70 patients with FEP reported that a longer time to remission was associated with abnormalities in the lateral and third ventricle (Lieberman et al., 1993). Another study of 26 FEP patients investigated early treatment response to haloperidol in a voxel-wide search, reporting that improved positive and negative symptoms after just one week correlated with cortical grey matter (GM) volumes (Zipursky et al., 1998). However, GM was also influenced by the dose (greater GM associated with lower doses), highlighting the importance of considering dose when analysing and interpreting pharmacological brain imaging findings. Specific cortical regions have been found to predict outcome in some studies. Prasad and colleagues (2005) found that functional outcomes were predicted by dorsolateral PFC volumes in 27 antipsychotic-naïve FEP patients. Prefrontal regions were also implicated in another study, where poor outcome was associated with smaller left prefrontal volumes (Kasparek et al.,

2009). However, this relationship between PFC and outcome has not been replicated by all studies (Molina et al., 2003b).

Other studies have investigated subcortical regions. Li and colleagues (2012) reported a significant increase in GM volume in the right putamen of 42 medication-naïve FEP patients treated for 6 weeks with various antipsychotic medications. These changes during treatment positively correlated with a reduction in positive symptoms but this methodology did not use baseline brain scans to predict later outcome. However, larger striatothalamic volume has been associated with a good response in females but not males (Fung et al., 2014), although remission rates for men in this study were generally low.

Studies have also attempted to investigate brain structure measures other than simply volumetric changes. For example, greater frontal cortical asymmetry was found in FEP patients who later showed symptomatic improvements (Szeszko et al., 2012). Furthermore, in the same study a larger temporal cortex thickness was associated with a shorter time to response. Cortical gyrification has also been investigated, with FEP patients who did not respond after 12 weeks of treatment showing decreased gyrification in frontotemporal regions and the insula compared with responders at baseline (Palaniyappan et al., 2013).

It is possible that baseline differences in brain structure are not necessarily strongly predictive of clinical outcome, but that dynamic changes during the course of illness are important. For example, greater progressive grey matter loss during the first year of illness has been associated with worse outcome at 5 years, specifically greater severity of negative symptoms and less likelihood of living independently (Cahn et al., 2006). Consistent with this, a greater extent of progressive reduction in frontal white matter and associated ventricular enlargement in patients with schizophrenia has been shown to relate to worse outcomes for patients (Ho et al., 2003). Once again, negative symptoms were implicated rather than positive.

Classical analyses of neuroimaging data suffer from several problems, including multiple testing, the failure to treat the brain as distributed networks rather than localised nodes of specialist function, and acting at population-level rather than the individual. Deficits in schizophrenia are likely to represent distributed, subtle alterations in the functioning of such networks, rather than focal lesions (Orru et al., 2012). Furthermore, generalising group-level results to individuals is problematic, as it treats patients as though they are homogeneous, ignoring potential variation amongst individuals. Recent techniques derived from pattern recognition methods, such as support vector machine learning (SVM) are now being investigated to address some of these problems. Pattern recognition techniques model brain activity as activation within distributed networks, which act in concert to guide behaviour (Zhang et al., 2012). This multivariate technique treats the data as spatial or spatio-temporal patterns, and is sensitive to correlations between voxels. Moreover, it can be used at an individual level, and is being studied for the purpose of diagnostic and prognostic prediction.

SVM may provide further clinical utility where it can predict prognosis (e.g. transition to psychosis in UHR individuals) or outcomes to treatment, if it can do so with a high degree of accuracy. Studies have shown promise for SVM to predict transition to psychosis using structural MRI (Koutsouleris et al., 2009; 2012), by differentiating those who transition to psychosis and those who do not, as well as differentiating each of these groups from healthy controls. One study has applied SVM to structural MRI to predict later outcomes for FEP patients (Mourao-Miranda et al., 2011). In this study, 100 patients were scanned at their first presentation. They were followed up on average 6.2 years later, and categorised into good and poor outcome according to their illness course type (poor outcome characterised by continuous illness and good outcome characterised by episodic illness). The authors reported that patients later categorised as having a continuous course could be distinguished at baseline from patients with a later episodic course with 70% accuracy. The regions that contributed to the classification most including the cingulate, parahippocampal gyri, basal ganglia,

and thalami. These results suggest that when patients first present, patterns in MRI data can be used to predict later outcomes at the individual level, with relatively high levels of accuracy. This study suggests that MRI data has potential value as a predictor of later outcome in individual patients. No studies so far have used SVM with structural imaging to predict treatment response, defined a priori.

Studies already carried out hold promise that SVM could be used to discriminate treatment responders from non-responders. However, it is still a relatively novel approach and as such further work is necessary to determine which modalities provide the greatest accuracy of prediction. However, this technique is likely to have high clinical translation value as predicting response to treatment creates the possibility that individual brain scans could be used to design personalised treatment plans based on individual neurobiological profiles (MacQueen, 2010).

In summary, results from studies investigating the relationship between brain structure and treatment response vary. Inconsistencies may result from methodological differences, whilst some studies suggest that dynamic changes rather than static baseline structure are more important in prediction. However, given the failure to find accurate, replicable, and reliable structural predictors of treatment response, many researchers have turned to functional imaging, which is emerging as a promising source of predictive biomarkers (Lawrie et al., 2011).

1.6.4.4.2 Functional imaging predictors of treatment response

Various imaging techniques can probe different aspects of brain function. To date, the technique most widely used to predict antipsychotic treatment response is PET, although other perfusion, functional and chemical imaging techniques have also been used, such as ASL, fMRI BOLD, and MRS.

Using PET, Kapur and colleagues (2001) used CGI scores to designate 22 antipsychotic-naïve or minimally treated patients as responders (CGI ≤ 2) or non-

responders (CGI ≥ 3) after two weeks of haloperidol treatment. They reported greater D2 receptor occupancy in responders than in non-responders, and suggested an optimal cut-off of 65% occupancy to differentiate between the two. This was consistent with a much earlier study reporting increased D2 receptor occupancy during treatment with raclopride was associated with a greater percentage reduction of BPRS (Nordstrom et al., 1993). Elsewhere, in 14 patients with recent onset psychosis, 2 weeks treatment with either risperidone or olanzapine lead to changes in PANSS positive scores that correlated with D2 receptor occupancy in striatal but not extra-striatal areas (Agid et al., 2007). However, occupancy related to neither negative symptoms nor baseline severity of symptoms. Both of these studies related functional changes *after* treatment initiation to treatment response. This does not provide a predictive measure that can be assessed prior to treatment initiation. However, these studies do suggest that response to antipsychotic medications is characterised by particular patterns of brain function, and elucidating such differences may reveal differing pathophysiology underlying disorders in those who respond well to current antipsychotics and those who do not.

Using a cross-sectional design, 12 treatment-resistant, 12 responders (determined using the Andreasen (2005) criteria), and 12 healthy controls were compared using PET (Demjaha et al., 2012). Patients were medicated with various different drugs but none were on clozapine. The authors reported elevated dopamine synthesis capacity in the striatum of responders compared with non-responders, as well as healthy controls. In contrast, non-responders did not differ from healthy controls. These results suggest that elevated dopamine in responders is targeted by current treatments. However, non-responders may have a different underlying pathophysiology, which affects systems other than dopamine and is not altered by current medications. This study is consistent with another that found elevated synaptic dopamine at baseline to predict good treatment response after 6 weeks of naturalistic treatment with antipsychotics (Abi-Dargham et al., 2000).

Fewer studies have investigated the utility of fMRI BOLD to predict treatment response in psychosis. A study of stable and medicated patients with schizophrenia, reported that greater activation in the dorsolateral PFC and cerebellum at higher cognitive loads during the n-back was associated with symptomatic improvement following CBT (Kumari et al., 2009). Other studies have shown a relationship between working memory-related activation and symptomatic improvement following antipsychotic medication. In patients treated with typical antipsychotics who were switched to 6 weeks risperidone, increased PFC activation during the n-back was related to improved negative symptoms (Honey et al., 1999). Similarly, increased ventrolateral PFC activation following 12 weeks of quetiapine has been associated with improvements in negative symptoms (Meisenzahl et al., 2006). However, again these studies do not predict outcomes using baseline measures and so are of limited predictive use.

To my knowledge, only two studies have predicted antipsychotic treatment response at baseline prior to treatment using fMRI (Van Veelen et al., 2011; Nejad et al., 2013). Van Veelan and colleagues investigated the relationship between dorsolateral PFC activation during working memory and treatment response to atypical antipsychotics, reporting that left dorsolateral PFC dysfunction in patients compared with controls was mainly due to non-responders, whereas responders did not differ from healthy controls in this region. Furthermore, reduced practice effects in the dorsolateral PFC at baseline predicted poor outcome at 10 weeks. In another study of working memory activation, Nejad and colleagues investigated functional connectivity in antipsychotic-naïve patients with FEP before and after 7 months of treatment with quetiapine (Nejad et al., 2013). They discovered a frontoparietal network that accurately predicted improvement in negative symptoms, and recognised the potential of using such information to stratify patients for treatment. Only one published study has investigated response to antipsychotic treatment (clozapine) in patients with schizophrenia using SVM and a measure of brain function. Responders and non-responders were discriminated using EEG with an accuracy of 86% (Khodayari-Rostamabad et al., 2010), suggesting that

functional imaging methods may hold promise as predictive biomarkers in machine learning approaches.

Studies have also investigated the use of brain perfusion to predict treatment response. Four studies have looked at rCBF in this manner (Rodriguez et al., 1996, 1997; Lahti et al., 2009; Ertugrul et al., 2009). These are described in detail in my paper included in Section 1.5.3. To summarise, various regions including the basal ganglia (including ventral striatum), thalamus, hippocampus, and frontal and parietal cortices have been implicated in prediction of treatment response. In these regions, baseline perfusion differences between patients and healthy controls are seen primarily in those who later respond to treatment, whereas non-responders do not differ from controls. Furthermore, over treatment the differences in these regions decreases in responders, such that they become more similar to healthy controls. Baseline thalamic and prefrontal perfusion (as a ratio of perfusion in the homolateral cerebellar hemisphere) predicted response correctly in 78.9% of cases (Rodriguez et al., 1997). Frontal/thalamic rCBF values have also been shown to predict percentage change in PANSS score after eight weeks of clozapine. Thus, previous research suggests that perfusion provides a promising potential predictive biomarker of treatment response. However, many studies have used patients with previous exposure to antipsychotics, making it difficult to assess whether the effects seen result from treatment withdrawal, chronic antipsychotic use, or the study drug.

In summary, PET studies have repeatedly shown a relationship between dopaminergic function and treatment response in psychosis. Research is yet to fully elucidate the potential for fMRI BOLD measures to predict response to treatment. Choosing relevant fMRI BOLD tasks is clearly important, to ensure that these tap a function that is impaired in patients with psychosis. Furthermore, we would expect functional activation that has been related to dopaminergic signalling to have greater potential as a predictive biomarker, given the results seen from PET imaging. Perfusion imaging offers further potential predictive biomarkers, although relatively few studies have been

carried out to date. In this study, I investigate salience processing, which is impaired in schizophrenia, and is thought to be caused by dysregulated dopamine firing and which is improved by current antipsychotic treatments (Kapur et al., 2005). I also investigate the ability of cerebral blood flow to predict treatment response in FEP minimally-treated patients. A strength of this work is the use of multiple imaging modalities in the same sample, at the same time points. This may provide a further predictive model in which these measures could be combined.

1.6.5 Multimodal imaging

The studies outlined above have investigated the potential of one particular brain imaging measure to predict treatment response. It is possible that the use of multiple modalities will improve prediction or be useful to stratify patients for clinical trials (Kempton and McGuire, 2014). It is easy to implement multiple modalities within an MRI scan by scanning the patient with different sequences. Some sites may also be able to implement both MRI and PET scans in the same patients, providing a variety of different, simultaneous, functional and structural measures. In a study using MRS and PET imaging of the same patients, elevated levels of glutamate in the anterior cingulate gyrus and normal presynaptic dopamine synthesis were associated with a poor response (Demjaha et al., 2014). Using two imaging techniques allows combinations of various factors (e.g. structural and perfusion alterations) that relate to a worse response to be identified. As suggested elsewhere, this could allow identification of poor responders, elucidating multimodal neurobiological predictions of treatment response, as well as providing insight into the relationship between imaging parameters in determining response to treatment (Kempton and McGuire, 2014).

1.6.6 Chapter summary and conclusions

In conclusion, the major implication from the evidence outlined in this chapter is that there are differences between the brains of responders and non-responders to antipsychotic medications, and that it might be possible to predict response using brain

imaging and multivariate approaches such as machine learning. The implication is that once predictive biomarkers of antipsychotic treatment response are fully elucidated they could be applied clinically, stratifying patients according to their likely response or personalising treatment by selecting an antipsychotic based on the results of a brain scan. These translational goals are a major long-term target of this area of research.

1.7 Conclusions and study rationale

The current literature reveals strong evidence that there are alterations in brain structure and function in schizophrenia, which may represent pathophysiology underlying the symptoms seen in the disorder. These neuropathological substrates represent targets for antipsychotic medications. Furthermore, increasing evidence suggests antipsychotic medications alter neurobiology, including brain structure, cerebral blood flow, and neural activation. It remains to be determined which neurobiological alterations are primary to the disease pathophysiology and which are secondary, resulting for example from antipsychotic treatment. Some neurobiological changes have been observed in responders but not in non-responders, and so understanding these alterations is key to elucidating factors underlying good (or poor) treatment response. This could inform mechanistic explanations for the remission of psychotic symptoms. In addition, identifying baseline differences in brain function and perfusion may allow prediction of later response to antipsychotic treatment. Given that response to treatment in this disorder is heterogeneous, a better understanding of brain changes related to the disorder and its treatment is warranted.

The objective of this study is to evaluate the effect of antipsychotic medications on brain perfusion (using cASL) and task-related neural activation (using fMRI). Furthermore, the study aims to elucidate whether any neurobiological markers of treatment response may be useful in the prediction of good or poor response to treatment. In addition, it provides a context within which the salience theory of psychosis can be investigated prospectively, illuminating the effects of antipsychotic medication on reward processing.

The work is carried out in patients experiencing their first episode of psychosis, in the early stages of the disorder (with a duration of untreated psychosis of less than two years), who are relatively naïve to antipsychotic treatment, and who are just initiating treatment with an antipsychotic according to the same, standardised protocol.

1.7.1 Aims and Objectives

This thesis aims to achieve the following:

1. Establish whether baseline differences in resting brain perfusion (measured with ASL), task-related activation (measured using fMRI during the SAT), and behavioural measures of salience attribution differ between antipsychotic-naïve or minimally treated FEP patients and healthy controls.
2. Establish whether four weeks treatment with amisulpride elicits an effect on resting brain perfusion, brain activation during the salience attribution task, and behavioural measures of salience attribution in patients.
3. Investigate how amisulpride-related alterations in resting brain perfusion and activation, relate to demographic, clinical, and behavioural measures of salience attribution.
4. Establish whether baseline measures of brain perfusion, task-related activation, and behavioural measures relate to subsequent treatment response at four and 12 weeks.

The long-term aim of such research is to elucidate the presence of individual variations in neurobiology that may act as reliable biomarkers for treatment response and thus facilitate a personalised approach to antipsychotic prescribing.

1.7.2 Hypotheses

Based on the reviewed literature, I hypothesised the following:

Good clinical response to the antipsychotic amisulpride (compared to poor response) will be associated with the following neurobiological changes:

At baseline –

a) Decreased dorsal striatal perfusion and increased frontal and hippocampal perfusion;

b) Aberrant salience attribution associated with increased ventral striatal and dorsolateral prefrontal cortex activation.

At four-week follow-up –

c) There will be an increase in resting dorsal striatal perfusion and a decrease in frontal and hippocampal perfusion;

d) There will be a normalization of aberrant salience processing and of the associated brain activation alterations.

2. METHODS

2.1 Study design

Minimally-treated or antipsychotic-naïve first episode psychosis (FEP) patients took part in a longitudinal, open-label intervention study, in which they underwent neuroimaging at baseline and again after treatment with an antipsychotic medication. The majority of patients (n=22) were recruited as part of OPTiMiSE (see below) to be treated with amisulpride under a standardised protocol. Other patients (n=3) were recruited as part of TreatFEP, in which they received naturalistic antipsychotic treatment, chosen by their clinical team. Healthy controls were recruited from the same catchment area to match patients in age, gender, ethnicity, and educational level.

2.1.1 OPTiMiSE clinical trial

The majority of data for this project were collected within the phase four clinical trial, 'Optimization of Treatment and Management of Schizophrenia in Europe' (OPTiMiSE). The aims of the trial are to provide evidence-based guidelines for drug therapy in FEP, to optimize current treatments, and to elucidate potential pathways for new treatments. To achieve these aims, a series of clinical studies and integrated experimental designs with imaging and genomic technologies are being used.

OPTiMiSE is a collaboration between 24 sites across Europe, and is funded by an FP7 grant of the European Commission. Eighteen European Psychiatric Institutes formed a consortium with the aim to recruit 350 antipsychotic-naïve or minimally treated (less than two weeks) patients at their first episode of schizophrenia over a period of six years. The Institute of Psychiatry, Psychology and Neuroscience is the Leader of the Work Package 1, which aimed to use structural MRI techniques in the optimisation of treatment. Structural MRI could be used both to exclude 'organic' psychosis and to aid prediction of treatment response based on underlying neuroanatomy. The patient

sample recruited at two UK sites (South London and Maudsley NHS Foundation Trust; SLAM (King's College London, KCL); and West London Mental Health NHS Trust; WLMHT) form the sample for the current project. The data for the current project were collected during Pharmacological Phase I of the OPTiMiSE protocol, the procedures for which are outlined below. Only patients at these two UK sites also underwent BOLD fMRI and arterial spin labelling in addition to structural scanning.

2.1.2 TreatFEP

Three patients recruited to the TreatFEP study were also included in my sample. The patient sample for this study was similar to OPTiMiSE in all aspects except a few subtle differences. These patients were not put on trial medication, but were about to be or had just (less than two weeks previously) been prescribed an antipsychotic by their clinical team. This study also did not limit the duration of untreated psychosis to two years, so patients may have been ill for longer than those recruited to OPTiMiSE (see detailed exclusion criteria below). TreatFEP patients underwent the same MRI procedure, and clinical and demographic information was collected at baseline and follow up with the same instruments. Inclusion of these patients increased the sample size and therefore increased the power of the analyses carried out.

2.1.3 Ethical approvals

Local ethical approval for OPTiMiSE at the Kings College London site was granted by the Psychiatry, Nursing & Midwifery Research Ethics Subcommittee (ref: 2011/052) and a separate approval was granted for neuroimaging protocols (ref(s): patients – R&D2011/050; healthy individuals - PNM/10/11-3). The West London Mental Health NHS Trust ethical approval was granted by London West Mental Health R&D Consortium (ref: MAREW1401). The TreatFEP study titled 'The neurobiology of schizophrenia and its relationship to treatment response' was granted ethical approval by the Psychiatry, Nursing & Midwifery Research Ethics Subcommittee (ref: 12/EE/0220).

2.2 Participants

A total of 47 participants were recruited to take part, of which 25 were patients and 22 were healthy controls.

2.2.1 Case definition and ascertainment

Cases were recruited from South London and the Maudsley (SLAM) Foundation Trust NHS Mental Health Services, including early intervention services, home treatment teams, liaison mental health teams and psychiatric wards. Recruitment was carried out over 4 years (from 2011 to 2015). Services were surveyed regularly by phone, email or face-to-face contact for new referrals meeting the inclusion criteria.

Further cases were recruited from West London Mental Health NHS Trust (WMLHT) by an OPTiMiSE study team working in this area. For these patients, the West London team carried out all recruitment, screening, and clinical assessments. However, all MRI scans were carried out at the SLAM (KCL) site at both baseline and follow up, such that patients were all scanned at all time points by the same scanner.

Participants were aged between 18 and 45, were residents of a London borough within the SLAM or WLMHT catchment areas, and during the recruitment period presented to local psychiatric services with a functional psychotic illness for the first time. As soon after first presentation as possible, when agreed upon by the responsible clinician (regarding ability to be interviewed and capacity to consent) potential participants underwent a full screening assessment to ascertain whether they met the specific inclusion criteria shown in Table 3.

Although patients were not excluded if they received evidence-based psychological therapies (e.g. CBT, family therapy), no patients were receiving this at the time of the study, although attended less-structured activity groups (for example to support management of social anxiety).

2.2.2 Healthy individual definition and ascertainment

Healthy individuals were recruited from within the same SLAM catchment area as patients by advertisements placed in local gyms, a local youth club, and online. Healthy participants were matched to the patient sample for age, gender, ethnicity, and educational level, and were excluded if they had a past diagnosis of neurological or psychiatric disorder.

Table 3: *Participant inclusion criteria*

	Inclusion criteria	Exclusion criteria
All	- Age 18–45 years; - Written informed consent.	- Presence of any contraindication to MRI scanning (e.g. implanted metallic object or electronic device)
Patients	- Diagnosis: DSM-IV schizophrenia, schizophreniform or schizoaffective disorder (on the basis of the Mini International Neuropsychiatric Interview Plus, M.I.N.I. Plus; Sheehan et al. 1998). Schizophreniform disorder was assessed through a M.I.N.I. diagnosis of psychosis (not otherwise specified) complemented by a diagnosis of schizophreniform disorder according to DSM-IV criteria; - Female patients of childbearing potential needed to utilize a proper method of contraception (the pill, vaginal ring, hormonal patch, intrauterine device, cervical cape, condom, contraceptive injection, diaphragm, abstinence).	- A time interval between the onset of psychosis and study entry exceeding two years; - Prior use of antipsychotic medication longer than two weeks in the previous year and/or six weeks lifetime; - Intolerance/contraindications to one of the study drugs; - Patients who were coercively treated at a psychiatric ward (based on a judicial ruling); - Patients who were represented by a legal guardian or under legal custody; - Pregnancy, as determined through a pregnancy test, or lactation.
Healthy controls	- Matched to the patient sample for age, gender, ethnicity, and education.	- A history of past diagnosis and/or treatment for neurological or psychiatric disorder.

2.2.3 Sample characteristics

All but one participant (n=46; 24 patients and 22 healthy controls) participated in the cASL component of the study at baseline, with 41 undergoing cASL at follow up (19 patients and 22 healthy controls). A subset of participants consented to take part in the fMRI component (n=43; 22 patients and 21 healthy controls), with 41 undergoing fMRI

at follow up (20 patients and 21 healthy controls). At recruitment, patients were minimally treated (all had received less than two weeks antipsychotic medication in the previous year, and less than six weeks in their lifetime). At baseline MRI, patients had received an average of 8.76 days (S.D. 7.74; range 0–24 days) of antipsychotic treatment. Patients receiving scans at two time points were scanned a mean 31.86 (S.D. 8.94) days after baseline.

The flow chart in Figure 4 and Table 4, illustrate the inclusion of patients in each part of the study, and the reasons for non-inclusion where relevant.

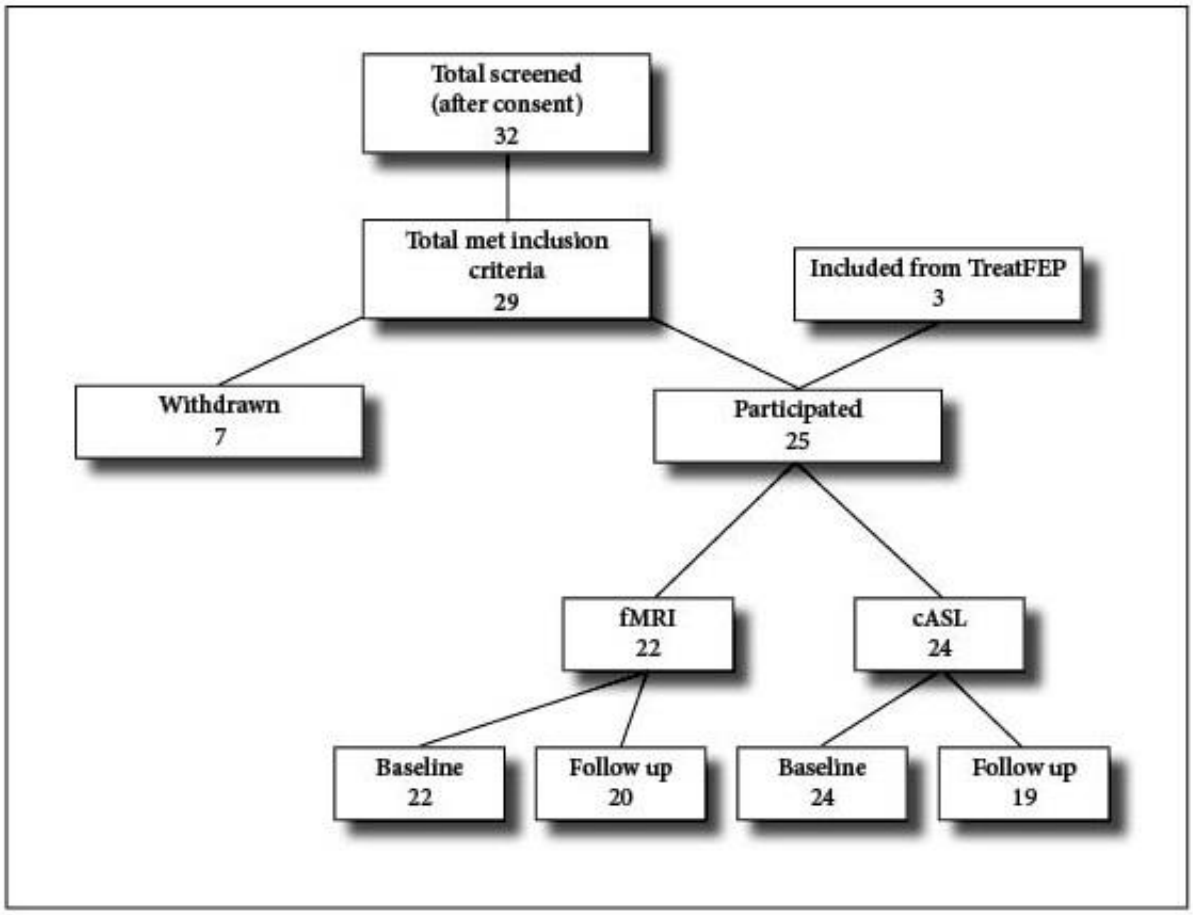

Figure 4: *Flow chart illustrating patients in each study component*

This flowchart illustrates the patients recruited for screening, and the final numbers in each group in the study. Details regarding reasons for withdrawal are given in the table below. Participants excluded from the analysis after data had been acquired are highlighted in the relevant results chapters.

Table 4: *Reasons for patient withdrawal*

Number of patients withdrawn	Reason for withdrawal
n=1	Personal reasons
n=2	Did not consent to MRI
n=1	Not eligible for MRI due to eye surgery
n=1	Too unwell
n=1	Did not want to take medication
n=1	Patient did not have time for study visits

Table 5 provides a summary of the baseline demographic characteristics for all patients and healthy controls (n=47), who took part in either scanning protocol or both. The majority of participants were male (72% of patients; 86.4% of healthy controls). Our patients had a mean age of 26.76 years (S.D. 5.31) and our healthy controls had a mean age of 24.91 years (S.D. 4.12). The majority of participants were white (40.0% of patients; 54.5% of healthy controls). Our patients had been ill for a mean 9.85 months (S.D. 10.58).

Patients and healthy participants did not differ significantly in age, gender, ethnicity or education level (all n.s., $p>0.05$). However, despite attempts to match our two groups, the healthy controls were more often employed ($\chi^2=4.397$, $p=0.038$) than were our patients. This might be expected given that the illness itself (including the prodromal period) may affect functioning, and therefore affects an individual's ability to complete or continue school or gain employment.

Table 5: *Demographic and clinical characteristics of all patients and healthy controls*

	Patients (n=25)	**Healthy controls (n=22)**
Gender (%)		
Female	28.0	13.6
Male	72.0	86.4
Age (years)		
Range	18–40	18–32
Mean	26.76	24.91
S.D.	5.31	4.12
Ethnicity (%)		
White	40.0	54.5
Black	36.0	22.7
Asian	16.0	13.6
Other	8.0	9.1
Employment (%)		
Employed	64.0	90.5
Unemployed	36.0	9.5
Education level (%)		
University (finished)	16.0	27.3
University (unfinished)	4.0	22.7
Professional training (finished)	16.0	9.1
Professional training (unfinished)	8.0	0.0
High school (finished)	36.0	40.9
High school (unfinished)	16.0	0.0
Less than high school	4.0	0.0
Missing	0.0	5.0
Diagnosis (%)		
Schizophrenia, undifferentiated	8.0	N/A
Schizophreniform disorder	28.0	
Schizoaffective disorder	4.0	
Schizophrenia, disorganised	4.0	
Schizophrenia, paranoid	48.0	
Schizophrenia, Other	8.0	
DUP (months)		
Mean	9.85	N/A
Range	0.5–44.0	
S.D.	10.58	
Antipsychotic administered (%)		
Amisulpride	88.0	N/A
Other (olanzapine n=2 and quetiapine n=1)	12.0	
*Max antipsychotic dose (mg)**		
Mean	172.11	N/A
S.D.	91.63	

* Dose stated in chlorpromazine equivalents.

2.2.4 Safety considerations

Several procedures were in place to ensure the safety of participants included in the study. Informed consent from patients was taken only by a psychiatrist, following an assessment of capacity to consent. Prior to the provision of study medication (amisulpride), we took patients for an ECG, which was performed and assessed for abnormalities by a cardiologist at King's College Hospital. This avoided known potential cardiac side effects of this medication. In addition, we monitored all side effects throughout study participation using the Udvalgfor Kliniske Undersogelser side effects scale (UKU). Patients met weekly with researchers during the provision of study medication, in addition to receiving usual care from their clinical teams. We ensured close communication between the study team and clinical teams regarding any adverse effects. Occurrences of serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARs) were closely monitored, and we followed strict reporting guidelines, according to local laws and regulations. All patients were provided with a card to carry with them, detailing their involvement in the trial and providing emergency contact numbers.

2.3 Procedures

2.3.1 Patient recruitment

All patients presenting to SLAM (or WLMHT) services with a FEP were identified and judged for eligibility in consultation with their clinical team. If suitable, patients were approached to participate in the study. Willing participants signed informed consent in the presence of a consultant psychiatrist who assessed for capacity to consent. Following this, we screened patients to ensure they met study inclusion and exclusion criteria (Table 3). Diagnosis of schizophrenia, schizophreniform disorder or schizoaffective disorder was confirmed using the Mini International Neuropsychiatric Interview (M.I.N.I) Plus (Sheehan et al., 1998). Those meeting study criteria underwent an ECG examination prior to drug administration and were cleared as normal by a cardiologist before initiating amisulpride. For patients recruited within TreatFEP, consent was obtained by a researcher, and the details of their antipsychotic treatment were recorded from clinical notes or discussion with their responsible clinician.

2.3.1.1 Baseline visit

Baseline assessments were carried out within a week of identifying the patient. During this visit, we completed the MRI scan, completed clinical assessments, and dispensed study medication (4 weeks open-label amisulpride), for those enrolled in OPTiMiSE. For these patients, the dose was increased gradually to a target of 400mg (in a split dose across the day) at day 12, following a specified titration schedule:

Day 0: 100mg (half a tablet)

Day 4: increase to 200mg

Day 8: increase to 300mg (one and a half tablets)

Day 12: increase to 400mg

Whilst the above guidelines were provided in the protocol, clinical teams determined the actual dose, based on their assessment of patient requirement. Variations to the specified schedule were permitted within the OPTiMiSE protocol but preferably a dose of 200, 400, 600 or 800 was reached by the end of 4 weeks (to ease potential transition to a double-blind phase, not relevant to the current project). Patients could not take any other antipsychotic during the study. However, concomitant medications of other kinds (mood stabilisers, benzodiazepines, antidepressants, and anticholinergic medications) were permitted but always recorded.

2.3.1.2 Demographic information

At the first visit, we recorded demographic variables including age, gender, ethnicity, marital status, occupation (past and present), parents' occupations, education, and current living arrangements. General clinical characteristics were recorded including DSM IV diagnostic category, duration of untreated psychosis (DUP; dated from first experience of psychotic symptoms as reported clinically up until first treatment, whether prescribed as part of the study or otherwise), treatment setting, and prognosis. In addition, data regarding alcohol and drug abuse, adverse events, concomitant medication, and drug accountability were collected throughout.

2.3.1.3 Clinical Measures

We completed several clinical assessments at baseline, as outlined below:

a) *Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987):* The PANSS is a well-validated measure of the symptoms of schizophrenia, and is the most widely used scale for this purpose. Ratings are based on a trained rater-led clinical interview of about 45 minutes. Three subsections are assessed: positive symptoms, negative symptoms, and general psychopathology. For each symptom, the rating takes into account both the presence and severity, as well as the degree to which it interferes in daily life. There is a total of 30 items, each of which is rated on a scale of 1 to 7,

representing absent through to extreme experience of each symptom. Therefore, scores range between 30 and 210. All raters underwent the same training, and were tested to ensure inter-rater reliability by the sponsor. The PANSS was used to monitor symptoms throughout the study and to determine remission status at follow up (see below).

b) *Clinical Global Impressions Scale of severity (CGI (severity); Guy, 1976):* The CGI is a 7-point scale representing the clinician's assessment of severity of a patient's illness. This is a subjective rating based on the clinician's past experience of individual's with the same diagnosis. Ratings are as follows: 1, normal, not at all ill; 2, borderline mentally ill; 3, mildly ill; 4, moderately ill; 5, markedly ill; 6, severely ill; or 7, extremely ill.

c) *Personal and Social Performance Scale (PSP; Morosini et al., 2000):* The PSP is a clinician-rated measure of personal and social dysfunction, rated in four areas: socially useful activities (work/study), personal and social relationships, self-care, and disturbing and aggressive behaviours. Each area is scored as absent, mild, manifest, marked, severe or very severe. A final score is then obtained from 1 – 100, according to specified criteria that take into account the frequency of problems, and the effects on functioning.

d) *Calgary Depression Scale for Schizophrenia (CDSS; Addington et al., 1992):* Levels of depression aside from negative symptoms or drug-induced side effects are rated using the CDSS. Nine categories are scored as 0, absent; 1, mild; 2, moderate; or 3, severe, to obtain a final score of between 0 and 27.

e) *Udvalgfor Kliniske Undersogelser side effects scale (UKU; Lingjaerde et al., 1987):* This assessment of drug-induced side effects was administered at baseline and weekly throughout the four-week antipsychotic treatment period. The UKU is a clinician-rated, 48 item, semi-structured interview, that rates the experience of side effects, independent of whether they are drug-induced. Experience of the side effect is rated

from 0 (“not or doubtfully present”), through 1, 2, and 3 which represent mild, moderate, and severe, respectively. Each item is also rated on the probability that it is caused by the medication (“impossible”, “possible” or “probable”), which can then inform the need for subsequent action. Side effect profiles can be assessed by the subscales for psychic, neurologic, autonomic, and other. A final ‘global assessment of interference by existing side effects with patient’s daily performance’ is assessed by the patient and the clinician.

2.3.1.4 Four-week follow up

At week four, patients were assessed for remission using the symptom remission criteria outlined by the Schizophrenia Working Group (Andreasen et al., 2005). Four weeks was chosen for pragmatic reasons, as a period in which stable treatment could be established. Remission was defined as a score of 3 or less (mildly present and does not interfere with daily life functioning) on the following PANSS items – delusions (P1), conceptual disorganisation (P2), hallucinations (P3), blunted affect (N1), passive/apathetic social withdrawal (N4), lack of spontaneity and flow of conversation (N6), mannerisms and posturing (G5) and unusual thought content (G9). A score of greater than 3 on any one of these items determined non-response. This operationalization of remission has shown good clinical validity and is associated with patient outcomes (e.g. Ciudad et al., 2009). The European First Episode Schizophrenia Trial (EUFEST) suggested that 40% of FEP patients reached these criteria within four weeks, suggested that it would be a realistic goal of antipsychotic treatment and within the timeframe of the current study. In addition to assessing remission, CGI (severity and improvement scores), PSP, CDSS, and UKU assessments were carried out at four week follow up.

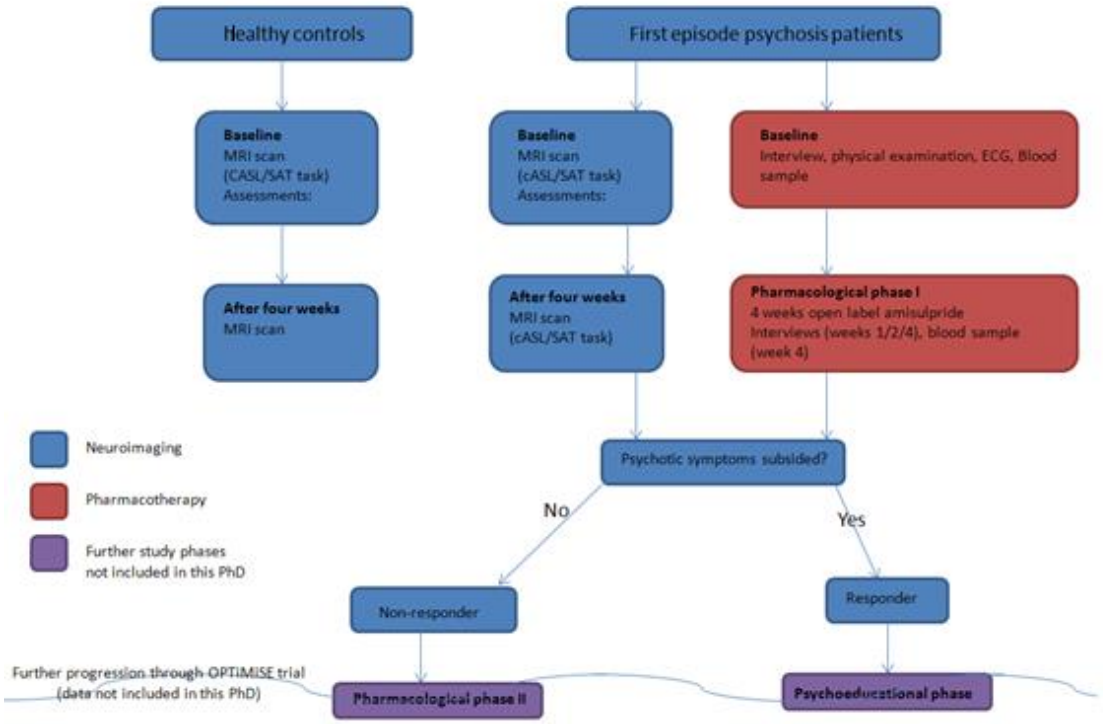

Figure 5: *Stages completed by patients in the OPTiMiSE trial, relevant to the current project*

Patients classed as in remission at four weeks remained on amisulpride, whilst those who were not in remission continued to a double-blind phase of the OPTiMiSE trial (not relevant to the current study). Between 4 and 12 weeks, all patients (for whom clinical notes were available) were medicated with a second generation antipsychotic. Of these, 57.1% remained on amisulpride (mean dose [chlorpromazine equivalent]: 115.63 mg). The remaining patients were treated with olanzapine (28.7%), aripiprazole (7.1%) or quetiapine (7.1%). The flow diagram in Figure 5 summarises the stages of the trial.

Given that there was a relatively small number of non-responders in the present study, I also calculated a continuous score of response at four weeks. This represented a percentage change in PANSS score between baseline and follow up, and was calculated according to the following formula:

$$\text{Percentage change in total PANSS} = \left(\frac{(\text{Baseline score} - 30) - (\text{Follow up score} - 30)}{(\text{Baseline score} - 30)} \right) \times 100$$

For individual PANSS items, the same formula was used but 7 rather than 30 was subtracted from the scores. In both cases, this subtraction accounted for the fact that a score of 7 for each individual item, or 30 for total scores, would be obtained with no psychopathology present.

2.3.1.5 Twelve-week follow up

To assess longer-term antipsychotic treatment response, I also assessed the clinical status of patients at 12 weeks. Again, this period was chosen for pragmatic reasons as suitable for completion of the Personal and Psychiatric History Schedule (PPHS). This clinical evaluation was completed using clinical notes as clinical measures, such as the PANSS, were not available for all patients. The PPHS is a standardized instrument developed by the World Health Organization (WHO) for use in multi-centre studies of incidence and outcome in schizophrenia (Jablensky et al., 1992). It assesses the presence and severity of a variety of symptoms, as well as the course of illness, and dysfunction in several related functional and occupational domains.

For current purposes, I was interested only in the items that related to the Andreasen criteria for remission using the PANSS. Seven items on the PPHS relate to the seven PANSS items listed in the remission criteria (see table 6), and therefore these were the items I used. I assessed all patients with a baseline MRI scan using the PPHS, regardless of whether or not they had 12-week follow up assessments. This allowed me to analyse, for those with both 12-week PANSS and PPHS assessments, the reliability of the PPHS in classifying response. This calculation suggested substantial agreement (kappa=0.667, p=0.014) (Landis and Koch, 1977).

Table 6: *PPHS items and their corresponding PANSS items (Jablensky et al., 1992)*

PPHS Item	PANSS Item
Delusions	*P1* – Delusions
Hallucinations	*P3* – Hallucinations
Thought Disorder	*G9* – Unusual thought content
Psychomotor Disorder	*G5* – Mannerisms and posturing
Flat Affect	*N1* – Blunted affect
Apathy	*N6* – Lack of spontaneity and flow of conversation
Social Withdrawal	*N4* – Social Withdrawal

Patient clinical information was accessed using the SLAM NHS Foundation Trust electronic Patient Journey System, on which clinicians record all contact with the patient concerned. Information is recorded only whilst patients remain under the care of services in this Trust, and therefore information was not available for some patients who had been transferred to care in a different Trust. In a period of one week prior to the 12-week interview date, I extracted any information relevant to the 7 items relating to the 7 PANSS remission criteria as outlined above. Where no notes were available for the calculated period, notes for the dates closest to this period were used. Rating of the 7 items followed the PPHS specified criteria. A score of 0 – 2 was recorded, where 0 indicated ‘absent’, 1 indicated ‘mild or occasional’, and 2 indicated ‘severe or frequent’.

To categorise patients as responders or non-responders according to the Andreasen criteria, PPHS ratings were converted to corresponding PANSS item scores as follows:

PPHS Rating	PANSS score
0	1, 2 or 3
1	5 or 6
2	7 or 8

Therefore, a responder at 12 weeks had a score of 0 in all the Andreasen items, which corresponds with a score of 3 (mild) or less on the PANSS. Non-responders had a score of either 1 or 2 in any one or more of the Andreasen items. This provided a 12-week categorisation of response to treatment.

2.3.2 Healthy controls

2.3.2.1 Baseline visit

Once identified and screened for study criteria (see Table 3), healthy controls underwent a brain scan with the same imaging protocol as for patients and using the same scanner. Healthy controls had no history of past diagnosis and/or treatment for neurological or psychiatric disorder.

2.3.2.2 Demographic information

At the first visit, demographic variables were recorded including age, gender, ethnicity, occupation, parents' occupations, and education. In addition, participants were asked about their caffeine and alcohol consumption, previous use of illicit substances, and any medication that there were currently taking.

2.3.3 Behavioural measures of salience attribution

The salience attribution task (SAT) was used to investigate salience attribution in all participants (Roiser et al. 2009). Initially, participants completed a tutorial out of the scanner to familiarise them with the task. A mean reaction time (RT) and standard deviation (SD) were also extracted from this tutorial to individually calibrate difficulty of the task in the scanner. The mean RT from the tutorial was used as the mean probe duration, calibrating difficulty to individual performance. The minimum and maximum probe duration was calculated using the SD (mean from practice +/- 2xSD). In the scanner, participants underwent another practice block before completing a single block of 64 trials. No rewards were available during the practice sessions.

The SAT is a speeded-response task offering monetary rewards and providing measures of salience attribution. Participants fixate on a cross and 1000ms later are presented with a cue either side of the cross in one of four categories (blue animals, red animals, blue household objects or red household objects). 1000–2000ms later, a black square (the probe) appears to which participants must respond as quickly as possible. The duration of the probe depends on the individual's reaction times during practice, as described above.

Following their response, written feedback is given. If they respond during presentation of the probe on a rewarded trial, they receive the message 'Good' or 'Very Quick', and information on how much money they have won. Should they respond before or after presentation of the probe, they receive the message 'Try to respond faster' or 'Missed', respectively. On trials that are unrewarded, where they respond during presentation of the probe they receive the message 'No money available'. Auditory feedback is also given, with the tone of the beep related to the amount won (higher beeps signalling larger amounts of money). Figure 6 illustrates the task.

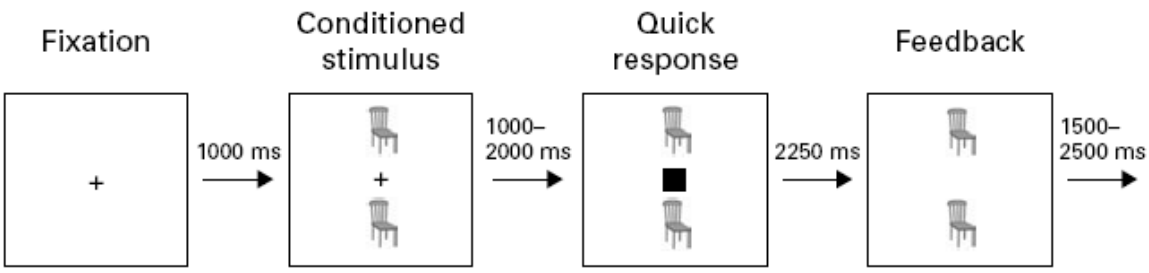

Figure 6: *Diagram showing a single trial in the SAT task.*

Fixation is followed by the conditioned stimulus. After a short delay, the participant must respond to the black square as quickly as possible. They then receive feedback as to how much money they have won in that trial.

In this task, half of all trials are rewarded with money (between 5 and 100 pence). Whether or not money is received depends on the stimulus presented before the probe, whilst the amount won depends on the speed of response (Table 7). Missed trials where money was available earn 5 pence. On trials in which participants respond during the presentation of the probe, the money won increases based on speed of response up to one pound.

There are four versions of the task, which each differ on the stimulus dimension that is rewarded (red, blue, animal or household object). In each of these, probability of reward is dependent on cue stimulus dimensions (colour or form) with money rewarded at a fixed probability for each stimuli combination. The task-relevant dimension is that in which the dimension categories differ in their relationship with reward, such that one category is rewarded on 87.5% of trials and the other on 12.5% of trials. The other dimension is task-irrelevant and rewarded equally, such that both stimulus categories are rewarded on 50% of trials. These probabilities remain constant for a full block of 64 trials. Table 8 illustrates this for a 'blue block'.

Table 7: *Feedback and reward given during the SAT*

Outcome on reinforced trials was determined by the speed of response to the probe. On non-reinforced trials, outcome was always the same, regardless of speed of response.

Trial Type	Response	Feedback	Reward
Reinforced	None/after probe	'Missed: five pence'	Five pence
	Premature – <100ms after probe onset	'Too early: five pence'	Five pence
	During probe but slower than mean RT	'Hit – good: ten pence'	Ten pence
	During probe and faster than mean RT by up to 1.5 SD	'Quick – very good: X pence'	$X = \frac{10+90 \times \left(\frac{\text{mean}}{RT} - \frac{\text{trial}}{RT} \right)}{(3 \times SD)}$
	During probe and faster than mean RT by more than 1.5 SD	'Very quick – excellent: X pence'	Up to max 100 pence
Non-reinforced	Any	'Sorry – no money available'	Zero pence

The different block types were numbered 1 to 4 and the choice of block type depended on the block that was used for the previous subject, in ascending order and circling back to 1 from 4. This meant that participants scanned at two time points may or may not receive the same block type.

Table 8: *Example of a 'blue block' in which colour is the relevant domain*

	Cue dimension	**Cue category**	**Rewarded (% trials)**
Task relevant	Colour	Blue	87.5
		Red	12.5
Task irrelevant	Form	Household objects	50
		Animals	50

The differential rewards depending on block type allow measures of both adaptive salience and aberrant salience to be obtained based on the participant's performance. Two measures are calculated, *adaptive and aberrant salience*, both of which are defined implicitly using reaction times (RT) to the probe and explicitly using visual analogue scale ratings (VAS). In the latter, after completing the task participants gave estimates of the percentage of time each stimulus category (blue, red, household objects, animals) were associated with reward. Responses where participants pressed the button prior to the probe (premature errors) and missed targets (omissions) are also recorded for each stimulus type. These measures represented the accuracy of participants, and allowed those making many mistakes to be excluded from the analysis (NB no participants had to be excluded for this reason).

Adaptive salience is the ability to correctly attribute salience to relevant stimuli. In this task, this is the ability to differentiate between the stimuli categories on the task-relevant dimension that are rewarded at high probability and those rewarded at low probability, disregarding the task-irrelevant dimension categories. Thus, adaptive implicit salience is calculated as RT on high probability-reinforcement trials relative to RT on low probability-reinforcement trials (collapsed across task-irrelevant stimulus

dimensions). Similarly, adaptive explicit salience is the increase in VAS rating for high probability-reinforcement trials relative to low probability-reinforcement trials (collapsed across task-irrelevant stimulus dimensions). This essentially shows whether participants respond differently to the stimulus categories that are relevant to reward in the expected direction. Thus, high scores of adaptive salience will be achieved by having lower RT to the high probability of reward category (e.g. responding more quickly to blue stimuli in a 'blue block') or rating the rewarded category as more associated with reward on the VAS. Responding equally or responding to the low probability of reward category more quickly will result in zero or negative adaptive salience scores, respectively.

For aberrant salience scores, the direction of difference is unimportant because any deviation from equal response (either in RT or VAS rating) shows an aberrant attribution of salience. Therefore, aberrant implicit salience is the *absolute* difference in RT between the two levels of the task-irrelevant stimulus dimension (collapsed across the task-relevant stimulus dimension). Aberrant explicit salience is the absolute difference in VAS rating between the two levels of the task-irrelevant stimulus dimension (collapsed across the task-relevant stimulus dimension). This measure gives an indication of whether the participant is responding differentially to stimulus categories where they should not be (i.e. where the probability of reward is equal).

2.3.4 Magnetic Resonance Imaging Acquisition

Neuroimaging was carried out in a General Electric Signa HDX 3 Tesla scanner at the Centre for Neuroimaging Sciences, Institute of Psychiatry, Psychology and Neuroscience. Participants underwent a brain scan at two time points: baseline and four-weeks follow up. All scans for all participants were obtained using the same scanner for a scan time of approximately 15 minutes. Handedness of participants was not recorded, and this should be borne in mind when considering the results.

Prior to the scan, patients completed a tutorial on a laptop in preparation for the functional MRI task. During the scan, high-resolution structural T1 images, functional MRI (EPI) BOLD images, and continuous arterial spin labelling images of CBF at rest were obtained. Structural images were acquired first, followed by functional images, and finally CBF images. During scan acquisition, four dummy scans were acquired to allow for T1 saturation. These were not recorded or included in the analysis.

2.3.4.1 Structural MRI

Structural data collected were 3D T1-weighted sagittal images, using a MP-RAGE sequence based on the protocol from the Alzheimer's Disease Neuroimaging Initiative (ADNI). (http://adni-info.org/.) This provided high-resolution whole brain T1-weighted images to facilitate co-registration and normalisation of the BOLD fMRI and cASL data.

2.3.4.2 BOLD fMRI

Images depicting BOLD contrast were acquired during the SAT to investigate neural correlates of salience attribution. Fifty slices of 2.4mm thickness were acquired to produce 237 volumes across the task. A TR of 2500ms and TE of 25ms were used throughout the task. The task was projected onto a screen, which participants viewed via a prismatic mirror.

2.3.4.3 Continuous Arterial Spin Labelling

The projector used during fMRI BOLD was switched off prior to the resting continuous arterial spin labelling (cASL) protocol, during which participants were told to rest awake with their eyes open. cASL is used to image CBF. This method uses a continuous inversion pulse to magnetically label flowing blood in the regions of interest. Perfusion-weighted images are produced by subtraction of a labelled image (with magnetically tagged inflowing blood) and a control image (in which inflowing blood has not been magnetically tagged). The result of this computation represents the amount of blood in a brain region at a particular point in time (ml/100g/min). Images were obtained using a

pseudo-continuous flow-driven, adiabatic inversion scheme and a 3D interleaved spiral FSE readout. We acquired 64 slices of 3mm thickness using a TR of 5500ms and a TE of 32.256ms.

2.3.5 Data Analysis

2.3.5.1 Clinical and behavioural data

Analysis of behavioural and demographic data was carried out in the Statistical Package for the Social Sciences (SPSS 16: SPSS Inc., Chicago, IL), which was also used to explore relationships between these variables and the imaging data. Initial descriptive statistics were used to explore the data and assess normality and the existence of outliers. Non-normal clinical data were transformed to improve normality or explored using non-parametric statistics, where appropriate.

Following the calculation of salience behavioural measures, as outlined above, the data was subjected to a one-sample t-test against 0 to investigate the acquisition of reward contingencies. The effect of omission errors and premature responses was assessed using repeated measures t-tests. Non-normal data were transformed using a square-root transformation before analysis. Untransformed scores are presented in this thesis for clarity and ease of interpretation.

Comparisons of patients and healthy controls were carried out using independent samples t-tests to assess whether the groups differ on measures of salience, both at baseline and follow-up. Further, paired samples t-tests were used to assess changes in salience scores from baseline to follow-up within patients. Where ANOVAs were used, equality of variance amongst the factors was assessed using Mauchley's test of sphericity. Where the assumption of equality of variance was violated, corrected statistics are reported (Greenhouse Geisser). Post hoc planned comparisons were implemented where significant main effects existed following ANOVA, to characterise

the effect seen. Due to potential increased type 1 error rate from such post-hoc testing, Bonferroni corrections are reported.

Correlational analyses were conducted for behavioural variables that were significantly altered by the antipsychotic treatment. Relationships between clinical measures and behavioural performance were explored using Pearson's r, or Spearman's r where data were non-normal.

2.3.5.2 Image Analysis

All images were analysed in the Statistical Parametric Mapping suite (SPM, version 8), which was developed by the Functional Imaging Laboratory of University College London (www.fil.ion.ucl.ac.uk/spm). Where correlations or extracted values of CBF were explored the Statistical Package for the Social Sciences (SPSS, version 15.0) was used.

2.3.5.2.1 Preprocessing

Both cASL and fMRI images were pre-processed prior to the main analysis.

a) cASL

Normalisation parameters were derived using a high-resolution T1 structural scan. The rCBF images were normalised to standard MNI space in a three-step procedure using the ASLToolbox of SPM-5. Extra-cerebral signal was removed using the 'Brain Extraction Tool' (BET) of the Functional Software Library (FSL) (Smith, 2002). This produced a binary mask, which along with the stripped T1 image was co-registered with the rCBF image. Co-registered images were multiplied by the rCBF map to remove extra-cerebral signal from this image. The result of this process and the skull-stripped T1 image were co-registered onto the original structural scan. The original T1 scan was normalised to the MNI T1 template provided by SPM, and the transformation matrix resulting from this was applied to both the T1 and the rCBF images. Lastly,

manual quality assurance was carried out, before smoothing using a 10mm Gaussian kernel.

b) fMRI BOLD

Functional MRI images were reorientated to the anterior and posterior commissures (AC-PC). Initially, this was carried out manually using http://imaging.mrccbu.cam.ac.uk/imaging/FindingCommissures as a guide. Linear 6-parameter rigid body transformation was then used within-subjects to align all the scans in the time series with one another. Images were first aligned to each other, then to a mean image from the time series. This produced movement parameters, which were used as covariates in the first level analysis.

A halfway registration process was used to provide a structural scan for co-registration with the EPI images using the longitudinal pairwise registration tool in SPM-12. Antipsychotic treatment has been associated with changes in structural brain imaging parameters and so halfway registration provides a mean between the baseline and follow up scans for each individual. Using this image to co-register with the EPI time series from baseline and follow up scans ensures that changes observed are due to functional alterations and not to structural changes. The normalised halfway structural scan was co-registered with the EPI time series, to allow the application of normalisation parameters to the EPI images. Finally images were smoothed using a Gaussian kernel of 10mm.

Movement was assessed using a script developed locally to provide plots of movement across the fMRI time course, which were assessed manually. Scans with large amounts of movement were submitted to a process of movement correction or discarded if necessary. Interpolation was used to correct for large spikes by taking the mean of the two images either side of a spike, and replacing the appropriate image.

2.3.5.2.2 cASL Image Analysis

cASL data were analysed using a fixed effects general linear regression model conducted with the locally developed ASLToolbox extension to SPM-5. T-tests were used to compare resting perfusion between groups and the effect of antipsychotic medications longitudinally within patients. Global perfusion was included as a covariate in this model. A priori ROIs, defined using wfupickup atlas, were explored based on previous studies investigating the changes elicited by antipsychotic treatment, including the hippocampus, caudate, and putamen (Rodriguez et al., 1996, 1997; Lahti et al., 2009; Ertugrul et al., 2009; Goozee et al., 2014). Mean perfusion values were extracted using the wfupickup atlas to define regions and functions in the ASLToolbox to extract mean values.

Clusters of regions in which I detected significant differences (between-subjects) or significant alterations with treatment (within-subjects) in rCBF were extracted. Using these clusters, I explored correlations with clinical and behavioural measures.

2.3.5.2.3 fMRI Image Analysis

Event-related univariate analysis was used to detect individual predictors of treatment response at baseline. Baseline measures were compared between those subsequently classified as responders and those classified as non-responders.

The fMRI images were evaluated in an event-related design with SPM8 in the context of the general linear model. Following realignment, normalization and smoothing, a GLM was built with a regressor for each cue and a regressor for the outcome. For each participant, a contrast image of activity related to adaptive reward prediction and another of aberrant reward prediction was produced. Second-level group differences were calculated from the results of the first-level analysis. As well as a whole brain analysis, regions of interest (ROIs), chosen on the basis of findings from Roiser's group (Roiser et al., 2012, Roiser et al., 2010), were investigated in the hippocampus,

striatum, and PFC. ROIs were identified using the wfupickatlas tool of SPM and were tested bilaterally. Images were corrected for multiple comparisons using FWE-correction with $p<0.001$. Following procedures developed by Roiser and his colleagues, cues for which participants fail to respond entirely were excluded, as they may result from a lack of attention during the trial (Roiser et al., 2009).

2.3.6 Power calculations

2.3.6.1 Power calculation for cASL

Previous research has shown that 12–18 patients are sufficient to detect a 10% change in perfusion in placebo-controlled crossover designs (the striatal size of change observed following haloperidol administration) (Murphy et al, 2011). This is consistent with findings from our group of highly statistically significant changes in rCBF using whole-brain ASL in just 18 subjects. Therefore, at the region of interest level, a sample only 18 subjects would be sufficient to detect a significant ($p<0.05$) 10% difference in between-group CBF means. This sample size is smaller than I had at baseline and follow up.

2.3.6.2 Power calculation for fMRI

A sample size of 16 participants is required to have 80% power at $p=0.05$ to detect an effect size of 0.9, between response groups at baseline on the SAT. This is less than the effect reported by Roiser et al. (2009) comparing patients with and without positive psychotic symptoms ($d=1.6$).

In the responder group alone, we would have 96% power to detect normalization of the SAT up to 4 weeks. The sample sizes in consideration are discussed at page 287 of the Discussion.

3. RESULTS

3.1 The effects of antipsychotics on clinical measures

In this chapter, I report the clinical characteristics and changes in clinical presentation of patients in my study. I first present clinical measures for the whole patient group, describing their clinical characteristics at baseline and follow up, and then changes to these measures over four weeks of antipsychotic treatment.

I next present the clinical characteristics of patients, separated according to treatment response at four weeks. I present cross-sectional comparisons of responders and non-responders at baseline and at follow up, and longitudinal effects of antipsychotic medication on clinical measures in each group after four weeks treatment. I also investigate any relationships between the demographics and sample characteristics and response to antipsychotic treatment at four weeks. The number of non-responders in my sample was small. As such, in addition to categorical comparisons of response I also assess relationships between the demographic and clinical characteristics and a continuous measure of response, the PANSS percentage change score.

Finally, to assess longer-term outcomes, I present clinical follow-up data at 12 weeks. I explore relationships between the demographic and clinical characteristics at baseline and follow up and clinical variables at 12 weeks. For patients without 12-week follow up PANSS scores, I used the PPHS to obtain scores from clinical notes where available (see page 122 of Methods for details). Where participants are not included in any analyses, I provide details as to the number of participants and the reasons for their non-inclusion.

I expected to see improvement in clinical symptoms over time, with greater improvements demonstrated in the treatment responders. I expected a good response

to be associated with female gender, a shorter DUP, and less severe symptom presentation at baseline.

3.1.1. Demographic and clinical characteristics of patients

Clinical symptoms were assessed at baseline and follow up (after four weeks of treatment) using the PANSS, CGI (severity), PSP, and CDSS (Table 9). A follow-up PANSS assessment was completed for all 25 patients to determine response to treatment, but not all patients completed the other clinical assessments. Numbers for each measure are provided in the appropriate section below. Demographic measures for the entire patient group are provided in the description of the sample, Table 5, Methods, page 115.

3.1.1.1 Clinical characteristics of patients at baseline

Clinical characteristics of the whole patient group (n=25) at baseline are shown in Table 9. Before treatment, patients had a mean total PANSS score of 65.76 (S.D. 14.16) and the majority were designated by the CGI as “moderately ill” (52.0%). The group had a mean PSP score of 53.86 (S.D. 11.79), indicating varying degrees of difficulty in daily functioning but not so low as to require intensive supervision (Morosini et al., 2000). Depressive symptom scores were relatively low, with a mean CDSS score of 4.41 (S.D. 3.65).

My sample differs from some samples in previous longitudinal imaging studies that have investigated treatment response. This is partly due to the aims of this study to recruit FEP patients who have not been previously treated. This means that patients were in general younger and less severely ill than many previous samples (e.g. Rodriguez et al., 1996, 1997; Ertugrul et al., 2009).

3.1.1.2 Clinical characteristics of patients at follow up

Table 9 shows the clinical characteristics of the whole patient group (n=25) at follow up following four weeks of antipsychotic treatment. At follow up, patients had a mean total PANSS score of 50.32 (S.D. 19.05) and most were designated as “mildly ill”, “borderline mentally ill” or “normal/not ill at all” (68.0%) on the CGI. Most patients were considered “very much improved” (28.0%) or “much improved” (36.0%) using the CGI improvement scale. The mean PSP score was 69.35 (S.D. 14.73), not far off the threshold of 71 for mild degree of difficulties in functioning. As at baseline, depressive symptom scores were low, with a mean CDSS of 3.11 (S.D.3.93).

Table 9: *Clinical scores for total patient group at baseline and 4-week follow up*

Patients	Baseline	Follow up (4 weeks)
PANSS, mean (SD)	(n=25)	(n=25)
Positive	19.16 (5.08)	12.00 (5.30)
Negative	14.28 (4.89)	12.52 (6.19)
General psychopathology	32.32 (6.84)	25.80 (8.92)
Total	65.76 (14.16)	50.32 (19.05)
CGI severity (%)	(n=22)	(n=22)
Normal/Not ill at all	0.0	28.0
Borderline mentally ill	4.0	20.0
Mildly ill	16.0	20.0
Moderately ill	52.0	8.0
Markedly ill	12.0	4.0
Severely ill	4.0	0.0
Missing	12.0	20.0
CGI improvement (%)		
Very much improved	-	28.0
Much improved	-	36.0
No change	-	8.0
Minimally worse	-	8.0
Missing	-	20.0
PSP (mean, SD)	(n=22) 53.86 (11.79)	(n=21) 69.35 (14.74)
CDSS (mean, SD)	(n=22) 4.41 (3.65)	(n=20) 3.11 (3.93)

3.1.1.3 Longitudinal effects of four-week antipsychotic treatment on clinical measures in patients

Here, I assess the effect of antipsychotic treatment on the clinical presentation of the entire patient group, comparing scores in symptom measures at baseline and follow up.

a) PANSS

(i) Raw scores

For the whole patient group, there was a decrease in positive, negative, and general psychopathology scores over the four weeks of antipsychotic treatment. As the data were not normally distributed, I conducted nonparametric Wilcoxon signed-rank tests to see whether these changes were significant. The results showed statistically significant decreases in positive ($Z=-3.97$, $p<0.0001$), general psychopathology ($Z=-3.58$, $p<0.0001$), and total ($Z=-3.74$, $p<0.0001$) PANSS scores. However, the change in negative symptoms was not statistically significant ($Z=-1.65$, $p=0.099$).

These results suggest that amisulpride treatment in this patient group led to statistically significant improvements in overall symptoms, and that this improvement is primarily in positive and general psychopathology symptoms, but is not seen in negative symptoms.

(ii) Percent change scores

Percent change scores reflect the degree of change in PANSS scores over time, which can be more easily related to clinically significant change in symptoms than can raw scores. The relationship between changes on the PANSS and clinical presentation has been explored in a number of studies that related PANSS percent change scores with clinician-rated CGI scores (Cramer et al., 2001; Leucht et al., 2005 a/b). These studies

suggest that change scores of between 19% and 28% correspond to “minimally improved”, whilst 40% to 53% corresponds to “much improved”.

In our total sample, there was a mean change of 60.94%, 19.31%, 25.00%, and 46.07% in positive, negative, general psychopathology, and total scores, respectively. Wilcoxon signed-rank test against 0 suggests that all of these changes were statistically significant (positive: $p<0.0001$; negative: $p=0.032$; general psychopathology: $p<0.0001$; total: $p<0.0001$). Clinically, these changes suggest less than “minimal improvement” in negative and general psychopathology scores, whilst positive and total PANSS scores were “much improved”.

In agreement with the results from the raw scores, these data suggest that amisulpride treatment in this patient group leads to statistically and clinically significant improvements in positive symptoms, but less improvement in general psychopathology symptoms. They suggest more modest but statistically significant changes in negative symptoms. Overall, there is an improvement in psychotic symptomatology for the patient group as a whole.

b) CGI

At baseline, the majority of patients scored 4 (“moderately ill”) or above on the CGI, whilst at follow up, the majority of patients scored 3 (“mildly ill”) or below. There was a decrease in median score from 4.87 (S.D. 1.14; “mildly ill”) to 3.23 (S.D. 1.21; “borderline mentally ill”), indicating a decrease in illness severity. Scores were non-normally distributed so non-parametric tests were employed. Following four weeks antipsychotic treatment, Wilcoxon signed-rank tests suggested a significant decrease in the CGI severity scores ($Z=-3.53$, $p<0.0001$). Furthermore, the majority of patients (64.0%) had a CGI improvement score of either 2 or 1, indicating they were “much improved” or “very much improved”, respectively.

The changes in CGI scores across four weeks of treatment support the patterns seen in PANSS scores, with a general improvement of symptoms for all patients, such that the severity of illness lessened with treatment.

c) PSP

Four weeks of antipsychotic treatment led to an increase in PSP total score, from 53.86 (S.D. 11.79) to 69.35 (S.D. 14.74), indicating an improvement in functioning. PSP scores were non-normally distributed and as such, I conducted a Wilcoxon signed-rank test, which indicated that this increase was statistically significant ($Z=-3.14$, $p=0.002$).

d) CDSS

Overall, there was a small decrease in CDSS scores from 4.41 (S.D. 3.65) to 3.11 (3.93), indicating a small improvement in symptoms of depression. However, a Wilcoxon signed-rank test revealed that this decrease was not statistically significant (n.s., $p>0.05$). The literature suggests that a score of 6–7 on the CDSS indicates major depression, whilst a score of 4–5 indicates minor depression (Bressan et al., 1998; Sarro et al., 2004). Patients in my sample were not very depressed and only just reached the threshold for minor depression even at baseline. Therefore, the lack of a significant change is probably due to a low level of depression symptoms experienced by the patients at any time point.

3.1.2 Demographic and clinical characteristics of responders and non-responders

In these sections, I present the demographic and clinical data for patients in relation to response to treatment at four and twelve weeks, to assess the associations of these variables with short- and longer-term treatment response.

3.1.2.1 Treatment response at four weeks

I conceptualised treatment response at four weeks in two ways. Firstly, as described in Methods (page 99), patients were categorised after four weeks treatment into

responders and non-responders using the Andreasen (2005) criteria. Secondly, I calculated percent change in PANSS scores for all patients at four weeks to provide a continuous measure of treatment response. I explored categorical data using Chi-squared tests. Where continuous data were normal, I conducted independent samples t-tests to investigate between group differences. Where data was non-normal, I employed nonparametric alternatives (e.g., Mann Whitney-U).

3.1.2.1.1 Cross-sectional comparisons of baseline demographic and clinical characteristics in four-week responders and non-responders

I first assessed whether there were any differences at baseline between future four-week responders and non-responders. Table 10 provides baseline demographic and clinical characteristics of these two groups. These data were investigated to assess whether those patients who were later categorised as a responder differed significantly from non-responders in demographics and baseline clinical measures.

Table 10: *Baseline demographic and clinical scores of 4-week responders and non-responders.*

Baseline characteristic	Responders (n=17)	Non-responders (n=8)
Gender (%)		
Female	35.3	12.5
Male	64.7	87.5
Age (years)		
Range	21 – 40	18 – 30
Mean (S.D.)	28.12 (5.21)	23.88 (4.55)
Ethnicity (%)		
White	35.3	50.0
Black	41.2	25.0
Asian	17.6	12.5
Other	5.9	12.5
Diagnosis (%)		
Schizophrenia, undifferentiated	0	25.0
Schizophreniform disorder	29.4	25.0
Schizoaffective disorder	5.9	0
Schizophrenia, disorganised	5.9	0
Schizophrenia, paranoid	47.1	50.0
Schizophrenia, Other	11.8	0
DUP (months) (mean, S.D.)	6.47 (6.82)	16.63 (13.76)
PANSS (mean, S.D.)		
Positive	17.65 (4.74)	22.38 (4.44)
Negative	13.00 (4.54)	17.00 (4.75)
General psychopathology	29.94 (6.79)	37.38 (3.50)
Total	60.59 (13.42)	76.75 (8.58)
CGI severity (%)	(n=17)	(n=8)
Normal/not ill at all	0.0	0.0
Borderline mentally ill	5.9	0.0
Mildly ill	23.5	0.0
Moderately ill	47.1	62.5
Markedly ill	5.9	25.0
Severely ill	5.9	0.0
Missing	11.8	12.5
PSP (mean, S.D.)	54.13 (13.73)	53.29 (6.80)
CDSS (mean, S.D.)	4.40 (3.94)	4.43 (3.21)
*Antipsychotic dose, mg (mean, S.D.)**	166.92 (42.50)	183.33 (160.20)

* Dose stated in chlorpromazine equivalents

a) Demographics

Four-week responders and non-responders did not differ significantly in terms of gender, diagnosis or ethnicity, nor did they differ in terms of employment level, education level or antipsychotic dose (all n.s., $p>0.05$). Whilst the mean age of responders was higher (28.12 years) than non-responders (23.88 years), this trend was not significant (n.s., $p=0.061$). Duration of untreated psychosis (months) was not normally distributed and so it was investigated using a non-parametric Mann Whitney-U test. This suggested that there was a significant difference in DUP between responders and non-responders ($Z=-2.07$, $p=0.038$), such that non-responders had been ill and untreated for longer than the responders.

b) PANSS

At baseline, four-week non-responders had significantly higher positive symptom scores ($t(23)=-2.37$ $p=0.027$), higher general psychopathology scores ($t(23)=-2.90$, $p=0.008$), and higher total PANSS scores ($t(23)=-3.10$, $p=0.005$) than responders. There was no significant difference between responders and non-responders on negative symptom scores ($t(23)=-2.03$, $p=0.055$).

b) CGI

Whilst non-responders had slightly higher mean CGI (severity) scores than responders at baseline, the difference in scores was not significant ($Z=-1.55$, $p=0.185$). Furthermore, a chi-square test for independence indicated no significant association between treatment response status and CGI scores ($X^2=4.74$, $p=0.32$).

c) PSP

Four-week responders and non-responders did not have significantly different PSP total scores ($Z=-0.72$, $p=0.490$) at baseline.

d) CDSS

Four-week responders and non-responders did not have significantly different CDSS scores at baseline (Z=-0.32, p=0.783).

3.1.2.1.2 Cross-sectional comparisons of demographic and clinical characteristics in 4-week responders and non-responders at follow up

I also assessed whether there were any differences between four-week responders and non-responders at follow up. Table 11 provides clinical measures at follow up for these two groups. As treatment response was determined by PANSS scores, I expected responders and non-responders to differ on this measure at follow up. However, I investigated all clinical scores at follow up, to assess whether responders and non-responders differed on all or only some measures of symptomatology.

a) PANSS

At follow up, PANSS scores were used to designate response to treatment. Therefore, as expected four-week non-responders had significantly higher scores than responders on all PANSS measures: positive (Z=-3.92, p<0.0001), negative (Z=-2.88, p=0.003), general psychopathology (Z=-3.65, p<0.0001), and total PANSS score (Z=-3.82, p<0.0001).

b) CGI

As expected, mean CGI (severity) scores at follow up were significantly different (Z=-3.13, p=0.001), suggesting non-responders were more ill than were responders. Furthermore, a Chi-square test for independence indicated a significant association between treatment response status and CGI scores (X^2=13.60, p=0.009).

There was also a significant difference in mean CGI (improvement) scores between responders and non-responders (Z=-2.44, p=0.019), with responders showing greater improvement. Again, a Chi-square test for independence indicated a significant

association between treatment response status and CGI improvement (X^2=9.04, p=0.029).

Table 11: *Clinical characteristics of 4-week responders and non-responders at 4-week follow up.*

Follow up characteristic	Responders	Non-responders
PANSS (mean, S.D.)	(n=16)	(n=8)
Positive	9.18 (2.21)	18.0 (4.96)
Negative	9.41 (2.00)	19.13 (7.00)
General psychopathology	21.24 (4.41)	35.50 (8.37)
Total	39.82 (7.12)	72.63 (17.08)
CGI severity (%)	(n=17)	(n=8)
Normal/Not ill at all	41.2	0.0
Borderline mentally ill	29.4	0.0
Mildly ill	17.6	25.0
Moderately ill	0.0	0.0
Markedly ill	0.0	12.5
Severely ill	0.0	0.0
Missing	11.8	37.5
CGI improvement (%)		
Very much improved	41.2	0.0
Much improved	31.2	25.0
No change	0.0	25.0
Minimally worse	5.9	12.5
Missing	11.8	37.5
PSP (mean, S.D.)	(n=15) 74.73 (12.20)	(n=5) 53.20 (8.73)
CDSS (mean, (S.D.)	(n=14) 2.50 (43.88)	(n=5) 4.80 (3.96)

c) PSP

At follow up, there was a significant difference in PSP scores between the groups (t(18)=3.62, p=0.002), with responders having a higher score indicative of better functioning.

d) CDSS

There was not a significant difference between responders and non-responders on CDSS scores at follow up (Z=-1.61, p=.273).

3.1.2.1.3 Associations between baseline demographic and clinical measures and a continuous measure of treatment response

As there were relatively few non-responders in our sample, I also assessed a continuous measure of treatment response in the form of percent change scores. This provides a continuous measure of the extent to which symptomatology changed in patients. As reported above, there were improvements in all subscales and total PANSS scores, with a mean change of 60.93% (S.D. 37.74), 19.31% (S.D. 84.12), 25.00% (S.D. 28.69), and 46.07% (S.D. 43.66) in positive, negative, general psychopathology, and total scores, respectively.

The following analyses assessed the association of baseline demographic and clinical measures with percent change in PANSS scores following treatment (as a continuous measure of response). Percent change scores were non-normally distributed and so non-parametric analyses were employed. Spearman's r was used to explore correlations and Mann Whitney-U or Kruskal-Wallis tests were used to explore the effects of categorical variables on percent change in PANSS.

a) Demographics

There was no relationship between age and percent change scores on the PANSS for any of the subscales or for the total PANSS score (all n.s., p>0.05). DUP showed a significant negative relationship with percent change in positive symptoms (r=-0.435, p=0.033), such that as DUP increased there was a decrease in the improvement of positive symptoms. This suggests that those with a longer DUP at baseline experience less improvement in their positive psychotic symptoms. There was a similar significant negative relationship between DUP and percent change in total PANSS score (r=-

0.453, p=0.026). This is likely driven by the change in positive scores as there were no significant correlations between DUP and percent change in negative (r=-0.378, p=0.069) or general psychopathology scores (r=-0.343, p=0.101). These results suggest that a shorter DUP is associated with a better response to treatment, manifested in an improvement in positive symptoms.

Percent change on total PANSS score and each subscale did not differ significantly between different ethnicities, DSM-IV diagnoses or education levels (all n.s., p>0.05). However, there was a significant difference in percent change in positive symptoms between employed and unemployed patients (Z=-2.072, p=0.038), but not on any other subscale or on total PANSS score. Employed patients showed a greater improvement in positive symptoms (median 87.5% change) than did unemployed patients (median 40.0% change).

b) PANSS

Total PANSS, positive, negative, and general psychopathology scores at baseline were not correlated with percent change in PANSS total or any subscale after four weeks' treatment (all n.s., p>0.05). This suggests that baseline severity of symptoms was not related to later degree of symptomatic improvement.

c) CGI

There was a significant relationship between CGI at baseline and percent change in total PANSS score (r=-0.47, p=0.028). There was no significant relationship between CGI at baseline and percent change in any PANSS subscale (all n.s., p>0.05).

d) PSP

There was no significant relationship between PSP total score at baseline and percent change in PANSS total or any PANSS subscale (all n.s., p>0.05).

e) CDSS

There was no significant relationship between CDSS total score at baseline and percent change in PANSS total or any PANSS subscale (all n.s., $p>0.05$).

3.1.2.1.4 Longitudinal effects of four-week antipsychotic treatment on clinical measures in four-week responders

I assessed the effect of four weeks of antipsychotic treatment on clinical measures in patients who went on to be designated as a responder at four weeks.

a) PANSS

(i) Raw scores

In four-week responders, there was a decrease in positive, negative, and general psychopathology scores over the four weeks of antipsychotic treatment. Due to non-normality of data, I performed nonparametric Wilcoxon signed-rank tests on positive symptoms scores, whereas all other changes were investigated using paired samples t-tests. The results showed statistically significant decreases in all scores: positive ($Z=-3.52$, $p<0.0001$), negative ($t(16)=2.99$, $p=0.009$), general psychopathology ($t(16)=5.53$, $p<0.0001$), and total ($t(16)=6.22$, $p<0.0001$) PANSS scores.

These results suggest that amisulpride treatment in responders led to statistically significant improvements in overall symptoms, with significant improvements in all subscales.

(ii) Percent change scores

As above, I calculated percent change scores to investigate the degree of change in scores over time in responders, which can be more easily related to clinically significant change in symptoms than can raw scores.

In four-week responders, there were mean changes of 77.90%, 44.88%, 34.76%, and 65.22% in positive, negative, general psychopathology, and total scores, respectively. Wilcoxon signed-rank test against 0 for non-normal data and one sample t-tests against 0 for normal data suggest that all of these changes were statistically significant (positive: $p<0.0001$; negative: $p=0.008$; general psychopathology: $t(16)=7.37$, $p<0.0001$; total: $t(16)=10.72$, $p<0.0001$). Clinically, all of these scores suggest that the changes in all PANSS scores were “much improved”.

In agreement with the results from the raw scores, these data suggest that amisulpride treatment in this patient group leads to statistically and clinically significant improvements in PANSS scores, with improvements in all subscales.

b) CGI

At baseline, the majority of patients who later showed a good response were given a score of 3 (“mildly ill”) or 4 (“moderately ill”) on the CGI. At follow up, all patients scored less than 3, with the majority scoring 1 (“normal/not ill at all”). Mean CGI scores showed a decrease with treatment from 4.81 (S.D. 0.24; “mildly ill”) to 2.73 (S.D. 0.21; “borderline mentally ill”), indicating a decrease in illness severity. Scores were non-normally distributed so non-parametric tests were employed. Following four weeks antipsychotic treatment, Wilcoxon signed-rank tests suggest a significant decrease in the CGI severity scores ($Z=-3.37$, $p=0.001$). Consistent with this, the majority (72.4%) of responders were given a CGI improvement score of either 2 or 1, indicating they were “much improved” or “very much improved”, respectively.

The changes in CGI scores across four weeks of treatment support the patterns seen in PANSS scores, with a general improvement of symptoms for responders, such that the severity of illness lessened with treatment.

c) PSP

In responders, four weeks of antipsychotic treatment led to an increase in PSP total score, from 54.13 (S.D. 3.54) to 74.73 (S.D. 3.15), indicating an improvement in functioning. PSP scores were non-normally distributed and as such, I conducted a Wilcoxon signed-rank test, which indicated that the increase was statistically significant (Z=-3.21, p=0.001).

d) CDSS

Responders showed a small decrease in CDSS scores from 4.50 (S.D. 1.09) to 2.50 (1.04), indicating a small improvement in symptoms of depression. Similarly to the whole patient group, this decrease was not statistically significant (Wilcoxon signed-rank test, n.s., p>0.05).

3.1.2.1.5 Longitudinal effects of four-week antipsychotic treatment on clinical measures in four-week non-responders

I assessed the effect of four weeks of antipsychotic treatment on clinical measures in patients who went on to be designated as a non-responder at four weeks.

a) PANSS

(i) Raw scores

In four-week non-responders, there appeared to be little change in PANSS scores. Positive, general psychopathology, and total PANSS scores showed negligible small decreases, whilst negative PANSS scores actually showed a slight increase after treatment. Paired sample t-tests suggest that there were no significant changes in positive, negative, general psychopathology or total PANSS scores (all n.s., p>0.05).

As expected, these results suggest that amisulpride treatment in this patient group did not lead to statistically significant improvements in overall symptoms and there were no

improvements on any subscale. This lack of improvement is reflected in the designation of these patients to the non-responders group.

(ii) Percent change scores

In non-responders, there were mean changes of 24.89%, -35.05%, 4.25%, and 5.38% in positive, negative, general psychopathology, and total scores, respectively. Wilcoxon signed-rank test against 0 for non-normal data and one sample t-tests against 0 for normal data suggest that all of these changes were not statistically significant (positive: $t(7) = 2.09$, $p=0.075$; negative: $p=0.499$; general psychopathology: $t(7)=0.34$, $p=0.74$; total: $p=0.26$). Clinically, all of these scores suggest that the changes in all PANSS scores were “minimally improved” or less. Negative symptoms worsened over the course of treatment.

In agreement with the results from the raw scores, these data suggest that amisulpride treatment in this group of non-responders did not lead to statistically or clinically significant improvements in symptoms, with no significant changes on any subscale.

b) CGI

At baseline, the majority of patients who later showed a poor response were given a score of 4 (“moderately ill”) or 5 (“markedly ill”) on the CGI. At follow up, most non-responders scored 3 (“mildly ill”) and none scored 1 (“normal/not ill at all”). Mean CGI scores did not show a significant change with treatment (baseline: 5.29, S.D.0.49; follow up: 4.80, S.D. 0.37; $p=0.62$). Improvement scores were more variable than in responders, with 25% showing much improvement, but 37.5% showing no change or worsening. Furthermore, the mean improvement score was 4.40 (S.D. 0.60), which indicates no change.

The lack of significant changes in CGI scores across four weeks of treatment support the patterns seen in PANSS scores, with little improvement in the symptoms of non-

responders, such that the severity of illness remained relatively stable despite treatment.

c) PSP

In non-responders, there was not a significant change in PSP score with treatment (baseline: 54.20, S.D. 3.96; follow up: 53.20, S.D. 8.73; p=0.78).

d) CDSS

Responders showed no change in CDSS scores, with the mean total score remaining stable at 4.80 throughout four weeks treatment.

3.1.2.2 Treatment response at 12 weeks

As described in Methods (page 122), remission status at 12 weeks after baseline was assessed using the PPHS. This allowed me to categorise patients into responders and non-responders at 12 weeks. Using this categorisation, I assessed the associations of demographic variables and baseline clinical scores with treatment response at 12 weeks. A continuous score was not available for this time point and so only categorical treatment response was explored. Categorical data were explored using chi-square tests. Where continuous data were normal, independent samples t-tests were applied to investigate between group differences. Where data was non-normal, nonparametric alternatives were employed (Mann Whitney-U).

PPHS scores were not available at 12 weeks for six patients (Table 12), as clinical notes were not available for these participants. All patients for whom data was not available at 12 weeks, were responders at four weeks. Data was available for PPHS assessment on all patients designated as non-responders at four weeks.

Table 12: *Reasons for non-inclusion at 12-weeks follow up*

Patient ID	Reason for non-inclusion
2208	Patient discharged to GP, no access to clinical notes.
2231	Patient not yet at 12 weeks.
TR33	Patient moved to another NHS Trust, no access to clinical notes.
2401	Patient recruited from another NHS Trust, no access to clinical notes.
2402	Patient recruited from another NHS Trust, no access to clinical notes.
2404	Patient recruited from another NHS Trust, no access to clinical notes.

Whilst at four weeks there were 17 responders (68.0%) and 8 non-responders (32.0%), at 12 weeks, there were 11 responders (58.0%) and 8 non-responders (42.0%). Response was relatively stable, with one responder at four weeks categorised as a non-responder at 12 weeks and one non-responder at four weeks categorised as a responder at 12 weeks. For all other participants, remission status was the same at 12 weeks as it was at four weeks.

Between four and 12 weeks, all patients (for whom clinical notes were available) were medicated with a second generation antipsychotic. Of these, 57.1% remained on amisulpride (mean dose [chlorpromazine equivalent]: 115.63 mg). The remaining patients were treated with olanzapine (28.7%), aripiprazole (7.1%) or quetiapine (7.1%).

3.1.2.2.1 Cross-sectional comparisons of demographic and clinical characteristics in 12-week responders and non-responders at baseline

Table 13 provides demographic and baseline clinical characteristics of the patient sample according to response to treatment at 12 weeks. These data were investigated to assess whether those patients who were categorised as a responder at 12 weeks differed significantly from non-responders at 12 weeks in demographics and baseline clinical measures.

a) Demographics

Twelve-week responders and non-responders did not differ significantly in terms of age, gender, diagnosis, ethnicity or education (n.s., $p>0.05$). Duration of untreated psychosis (months) was not normally distributed and so I investigated it using a non-parametric Mann Whitney-U test. DUP did not seem to be related with long-term response as there was no significant difference in DUP between 12-week responders and non-responders ($Z=-0.92$, $p=0.395$).

b) PANSS

At baseline, 12-week non-responders had significantly higher general psychopathology symptom scores ($t(17)=-4.07$, $p=0.001$) and total PANSS scores ($t(17)=-2.67$, $p=0.016$) than responders. There was no significant difference between 12-week responders and non-responders in either positive ($t(17)=-1.26$, $p=0.23$) or negative symptom scores ($t(17)=-1.15$, $p=0.27$).

c) CGI

There was no significant difference between 12-week responders and non-responders in baseline mean CGI scores ($Z=-1.84$, $p=0.13$). Furthermore, a chi-square test for independence indicated no significant association between twelve-week treatment response status and CGI scores ($X^2=3.74$, $p=0.29$).

d) PSP

There was no significant difference in PSP total score at baseline between 12-week responders and non-responders (Z=-0.75, p=0.48).

Table 13: Baseline d*emographic and clinical scores of 12-week responders and non-responders*

Baseline characteristic	Responders (n=11)	Non-responders (n=8)
Gender (%)		
Female	36.4	12.5
Male	63.6	87.5
Age (years)		
Range	21 – 34	18 – 32
Mean (S.D.)	27.18 (4.58)	25.25 (5.18)
Ethnicity (%)		
White	18.2	50.0
Black	54.5	25.0
Asian	9.1	25.0
Other	18.2	0.0
Diagnosis (%)		
Schizophrenia, undifferentiated	0.0	25.0
Schizophreniform disorder	27.3	37.5
Schizoaffective disorder	0.0	0.0
Schizophrenia, disorganised	0.0	0.0
Schizophrenia, paranoid	63.6	37.5
Schizophrenia, Other	9.1	0.0
DUP (months) (mean, S.D.)	9.05 (8.31)	14.13 (14.05)
PANSS (mean, S.D.)		
Positive	18.91 (5.45)	21.75 (3.85)
Negative	13.73 (4.43)	16.13 (4.55)
General psychopathology	29.18 (4.94)	38.88 (5.38)
Total	61.82 (13.93)	76.75 (8.58)
CGI severity (%)		
Normal/Not ill at all	0.0	0.0
Borderline mentally ill	0.0	0.0
Mildly ill	18.2	0.0
Moderately ill	63.6	50.0
Markedly ill	9.1	25.0
Severely ill	0.0	12.5
Missing	9.1	12.5
PSP (mean, S.D.)	54.80 (10.63)	50.43 (10.89)
CDSS (mean, S.D.)	4.20 (4.05)	5.14 (4.06)

e) CDSS

There was no significant difference in CDSS total score at baseline between 12-week responders and non-responders (Z=-0.59, p=0.60).

3.1.2.2.2 Cross-sectional comparisons of baseline demographic and clinical characteristics in 12-week responders and non-responders

I also investigated whether clinical scores after four weeks of treatment were significantly different, to assess whether there were differences already evident between 12-week responders and non-responders at this point (Table 14).

a) PANSS

When 12-week responders and non-responders were compared on PANSS scores after four weeks of treatment, non-responders had significantly higher positive symptoms scores (Z=-2.96, p=0.002), general psychopathology scores (Z=-2.52, p=0.009), and total PANSS scores (Z=-2.73, p=0.005) than responders. There was no significant difference between responders and non-responders in negative symptom scores (Z=-1.70, p=0.091).

b) CGI

As expected, mean CGI (severity) scores at follow up were significantly different (Z=-2.90, p=0.003), suggesting 12-week non-responders were more ill than were responders. Furthermore, a chi-square test for independence indicated a significant association between treatment response status and CGI scores (X^2=10.50, p=0.033).

There was, however, no significant difference in mean CGI (improvement) scores between responders and non-responders (Z=-1.13, p=0.25). Consistent with this, a Chi-square test for independence indicated no significant association between treatment response status and CGI improvement (X^2=5.52, p=0.14).

Table 14: *Clinical characteristics of 12-week responders and non-responders after four weeks of treatment*

Follow up characteristic	Responders (n=11)	Non-responders (n=8)
PANSS (mean, S.D.)		
Positive	9.73 (4.10)	16.75 (5.34)
Negative	11.45 (5.92)	16.88 (6.62)
General psychopathology	23.27 (7.16)	33.88 (8.63)
Total	44.45 (16.31)	67.50 (17.61)
CGI severity (%)		
Normal/Not ill at all	36.4	0.0
Borderline mentally ill	36.4	0.0
Mildly ill	18.2	25.0
Moderately ill	0.0	25.0
Markedly ill	0.0	12.5
Severely ill	0.0	0.0
Missing	9.1	37.5
CGI improvement (%)		
Very much improved	27.3	12.5
Much improved	54.5	12.5
No change	0.0	25.0
Minimally worse	9.1	12.5
Missing	9.1	37.5
PSP (mean, S.D.)	69.40 (15.35)	57.2 (5.85)
CDSS (mean, (S.D.)	3.4 (4.50)	4.4 (3.91)

c) PSP

There was no significant difference in PSP total score at four weeks follow up between 12-week responders and non-responders ($t(13)=1.69$, $p=0.12$).

d) CDSS

There was no significant difference in CDSS total score at four weeks follow up between 12-week responders and non-responders ($Z=-0.74$, $p=0.51$).

3.1.2.2.3 Longitudinal effects of four-week antipsychotic treatment on clinical measures in responders at twelve weeks

I assessed the effect of four weeks of antipsychotic treatment on clinical measures in patients who went on to be designated as a responder at 12 weeks.

a) PANSS

(i) Raw scores

In 12-week responders, there was a decrease in positive, negative, and general psychopathology scores over the four weeks of antipsychotic treatment. Due to non-normality of data, I conducted nonparametric Wilcoxon signed-rank tests on all scores. The results showed statistically significant decreases in positive ($Z=-2.94$, $p=0.003$), general psychopathology ($Z=-2.54$, $p=0.011$), and total ($Z=-2.80$, $p=0.005$) PANSS scores. The change in negative PANSS scores was not significant ($Z=-1.47$, $p=0.14$).

These results suggest that amisulpride treatment in 12-week responders led to statistically significant improvements in overall symptoms, with significant improvements in all subscales except for negative symptoms.

(ii) Percent change scores

As above, I calculated percent change scores to investigate the degree of change in scores over time in 12-week responders, which can be more easily related to clinically significant change in symptoms than can raw scores.

In these responders, there were mean changes of 79.87%, 29.88%, 27.15%, and 58.48% in positive, negative, general psychopathology, and total scores, respectively. Wilcoxon signed-rank test against 0 for non-normal data and one sample t-tests against 0 for normal data suggested that changes were statistically significant in positive ($p=0.003$), general psychopathology ($t(10)=3.97$, $p=0.003$) and total ($t(10)=5.97$, $p<0.0001$) PANSS scores. The mean change in negative symptoms was

not significant (t(10)=1.53, p=0.16). Clinically, these scores corresponded to “minimally improved” or “much improved”.

In agreement with the results from the raw scores, these data suggest that amisulpride treatment in this patient group leads to statistically and clinically significant improvements in overall PANSS scores, but not in negative symptoms.

b) CGI

At baseline, the majority of patients who later showed a good response at 12 weeks were given a score of 3 (“mildly ill”) or 4 (“moderately ill”) on the CGI. After four weeks of treatment, all patients scored less than 3. Mean CGI scores showed a decrease with treatment from 4.90 (S.D. 0.57; “moderately ill”) to 2.80 (S.D. 0.79; “borderline mentally ill”), indicating a decrease in illness severity. Scores were non-normally distributed so non-parametric tests were employed. Following four weeks antipsychotic treatment, Wilcoxon signed-rank tests suggest a significant decrease in the CGI severity scores (Z=-2.87, p=0.004). Consistent with this, the majority (81.8%) of responders were given a CGI improvement score of either 2 or 1, indicating they were “much improved” or “very much improved”, respectively.

The changes in CGI scores across four weeks of treatment support the patterns seen in PANSS scores, with a general improvement of symptoms for responders, such that the severity of illness lessened with treatment.

c) PSP

In 12-week responders, four weeks of antipsychotic treatment led to an increase in PSP total score, from 54.80 (S.D. 10.63) to 69.40 (S.D. 15.35), indicating an improvement in functioning. This represented a significant increase in PSP scores (t(9)=-2.34, p=0.044).

d) CDSS

Twelve-week responders showed a small decrease in CDSS scores from 4.20 (S.D. 4.05) to 3.40 (4.50), indicating a small improvement in symptoms of depression. As before, this decrease was not statistically significant (Wilcoxon signed-rank test, Z=-0.74, p=0.46).

3.1.2.2.4 Longitudinal effects of four-week antipsychotic treatment on clinical measures in 12-week non-responders

I assessed the effect of four weeks of antipsychotic treatment on clinical measures in patients who went on to be designated as a non-responder at 12 weeks.

a) PANSS

(i) Raw scores

In 12-week non-responders, there appeared to be little change in PANSS scores. Positive, general psychopathology, and total PANSS scores showed small or negligible changes after treatment. Paired sample t-tests suggest that there were no significant changes in positive, negative, general psychopathology or total PANSS scores (all n.s., p>0.05).

As expected, these results suggest that amisulpride treatment in this patient group did not lead to statistically significant improvements in overall symptoms and there were no improvements on any subscale. This lack of improvement is reflected in the designation of these patients to the non-responders group.

(ii) Percent change scores

In 12-week non-responders, there were mean changes of 30.10%, -21.66%, 12.05%, and 14.53% in positive, negative, general psychopathology, and total scores, respectively. Wilcoxon signed-rank test against 0 for non-normal data and one sample

t-tests against 0 for normal data suggest that all of these changes were not statistically significant (positive: t(7)=2.24, p=0.060; negative: p=0.87; general psychopathology: p=0.16; total: p=0.16). Clinically, all of these scores suggest that the changes in all PANSS scores were “minimally improved” or less. Negative symptoms worsened over the course of treatment.

In agreement with the results from the raw scores, these data suggest that amisulpride treatment in this group of non-responders did not lead to statistically or clinically significant improvements in symptoms, with no significant changes on any subscale.

b) CGI

At baseline, the majority of patients who later showed a poor response were given a score of 4 (“moderately ill”) or 5 (“markedly ill”) on the CGI. At follow up, most non-responders scored 3 (“mildly ill”) or worse and none scored 1 (“normal/not ill at all”). Mean CGI scores did not show a significant change with treatment (baseline: 5.40, S.D.0.89; follow up: 4.80, S.D. 0.84; p=0.41). Improvement scores were more variable than in responders, with 25% designated as much or very much improved, but 37.5% showing no change or worsening. Furthermore, the mean improvement score was 4.20 (S.D. 1.64), indicating no change.

The lack of significant changes in CGI scores across four weeks of treatment support the patterns seen in PANSS scores, with little improvement in the symptoms of non-responders, such that the severity of illness remained relatively stable despite treatment.

c) PSP

In 12-week non-responders, there was not a significant change in PSP score with treatment (baseline: 50.20, S.D. 11.30; follow up: 57.20, S.D. 5.85; t(4)=-1.12, p=0.33).

d) CDSS

Twelve-week non-responders showed a small decrease in CDSS scores, but this change was not significant (baseline: 5.80, S.D. 4.76; follow up: 4.40, S.D. 3.91; p=0.41).

3.1.3 Chapter summary

In this chapter, I have described the effects of antipsychotic treatment on clinical measures in patients with FEP. Furthermore, I have explored the relationships between baseline and four-week demographic/clinical factors and treatment response as assessed at four and 12 weeks. Four-week treatment response was assessed in two ways. Firstly, patients were divided categorically into responders and non-responders, according to the Andreasen criteria (Andreasen et al., 2005). Secondly, percent change in PANSS score was used as a continuous measure of treatment response. Grouping patients in this way is a novel approach, that can clarify the relationships between clinical measures and outcomes.

To summarise, in the entire patient group, symptoms improved with treatment, with significant decreases in all PANSS subscales, apart from negative symptoms. These improvements were confirmed by the mean percent change scores on the PANSS, as well as changes in CGI and PSP ratings. At an individual level, not all patients improved with treatment, with 17 (68%) showing a good response to treatment and 8 (32%) showing a poor response to treatment at four weeks.

Grouping patients according to response showed that not only was a shorter DUP associated with a better response to treatment, but there was also a significant difference between responders and non-responders, such that non-responders had a longer DUP. Comparisons of responders and non-responders also suggest that non-response was associated with a greater severity of illness at baseline. These results may indicate that early intervention, during a milder stage of the disorder, could lead to

better response. Alternatively, there may be differences in both the underlying pathophysiology and the resulting symptomatology observed that determines whether someone will respond or not to treatment.

3.2 The effects of antipsychotics on behavioural measures of salience attribution and related neural function measured using fMRI

In this chapter, I present behavioural and related neural function (fMRI) data for the salience attribution task in patients and healthy controls.

I begin by presenting behavioural data for antipsychotic-naïve patients and healthy controls. I assess these using cross-sectional comparisons to explore differences in salience measures before treatment and following four weeks of amisulpride treatment. I also present longitudinal analyses of behavioural measures to assess the effect of antipsychotic medication on measures of salience attribution in patients. Finally, I assess relationships between response to treatment (at four and 12 weeks) and measures of salience attribution.

In the second part of the chapter, I present data representing the neural function underlying salience attribution measured using fMRI in patients and healthy controls. I begin by presenting cross-sectional data comparing antipsychotic-naïve patients with healthy controls. This explores whether activation related to salience attribution in patients before treatment differs from that of healthy individuals (suggesting that potential differences seen may relate to illness pathophysiology). I then present a cross-sectional analysis of the neural function of patients after four weeks of treatment in comparison to that of healthy controls. This explores whether any differences between these groups, that may have been present at baseline, are still present following four weeks' treatment with amisulpride.

Subsequently, I present longitudinal analyses exploring the effect of antipsychotic medication on salience activation in patients. In these analyses, I compare SPM maps at baseline and follow up in the same patients. For completion, I also present longitudinal assessments of healthy individuals, comparing baseline and follow up scans for any altered patterns of neural function.

Next, I assess the relationship between antipsychotic treatment response at four weeks and salience activation. I do this by first exploring patterns of activation in responders and non-responders cross-sectionally at baseline and follow up (after four weeks of treatment), with one another and with healthy controls. I then assess longitudinal changes in neural function seen in each of these groups individually. Finally, to assess longer-term outcomes, I assess the relationship between neural activation and antipsychotic treatment response at 12 weeks, both cross-sectionally and longitudinally.

For all imaging analyses, I first evaluated global brain volumes, before assessing any regions of interest defined a priori. I discuss all effects surviving either voxel- or cluster-level family-wise error (FWE) correction for whole brain multiple comparisons.

Some participants did not consent to take part in the fMRI arm of the study (see Methods, Table 4, page 114 for reasons). Any participants who completed the fMRI protocol but are missing from an analysis are reported in each relevant section. Unless otherwise stated, all participants who completed the fMRI paradigm (n=22) were included in the analysis.

Hypotheses explored:

- At baseline, patients will show greater aberrant salience but reduced adaptive salience compared with healthy controls.
- Aberrant salience processing will be associated with ventral striatal and dorsolateral PFC activation.
- At follow up, there will be a normalisation of abnormal salience attribution and the associated activation, such that patients become more like healthy controls. However, this change will be specific to treatment responders, such that behavioural and neural measures in responders and non-responders differ at follow up. Patients who do not respond to treatment will continue to exhibit

altered salience attribution and ventral striatal activation to irrelevant stimulus features.

3.2.1 Salience attribution scores in patients and healthy controls

I first considered behavioural measures of salience attribution for the entire patient group and the healthy controls. These analyses try to identify any abnormalities in salience attribution processes in patients with FEP, which might support the salience attribution hypothesis. They also investigate the effects of antipsychotic treatment in a group of previously untreated patients with FEP.

I carried out cross-sectional comparisons of patients and healthy controls on measures of salience attribution (implicit aberrant and adaptive salience, explicit aberrant and adaptive salience, premature/omission errors, and money won) at baseline (where patients were minimally treated) and at follow up (after four weeks of antipsychotic treatment). I also investigated longitudinal changes in these measures in patients.

3.2.1.1 Cross-sectional comparisons of salience attribution scores in patients and healthy controls at baseline

Table 15 provides an overview of baseline SAT scores for patients and healthy controls.

At baseline, all participants responded more quickly on high- relative to low-probability reinforced trials ($t(42)=3.04$, $p=0.004$). Analysis of the groups separately revealed that healthy controls showed significant implicit adaptive salience ($t(20)=3.01$, $p=0.007$) but patients did not ($t(21)=1.40$, $p=0.18$).

Table 15: *Measures of salience attribution at baseline*

Salience measure	Patients (n=22)	Healthy controls (n=21)	Test, sig.
RT adaptive salience (ms)	8.24 (27.67)	16.47 (25.11)	t(41)=1.02, p=0.31
VAS adaptive salience (mm)	17.52 (31.69)	57.40 (32.87)	t(41)=-4.05, p<0.0001*
RT aberrant salience (ms)	19.52 (16.39)	14.41 (10.87)	t(41)=1.01, p=0.32
VAS aberrant salience (mm)	11.61 (10.89)	11.17 (9.51)	t(41)=0.14, p=0.89
Omission errors	0.50 (1.92)	0.33 (0.66)	Z=-0.83, p=0.41
Premature errors	2.45 (2.79)	1.43 (1.75)	Z=-1.31, p=0.19
Money won (£)	10.19 (4.30)	11.16 (5.46)	t(41)=-0.65, p=0.52

RT=reaction time; ms=milliseconds; VAS=visual analogue scale; mm=millimetres; * p<0.05

At baseline, patients had lower adaptive salience scores (implicit and explicit) and higher implicit aberrant salience scores than healthy controls, and similar explicit aberrant salience scores. However, the only significant group difference was for scores of explicit adaptive salience (t(41)=-4.051, p<0.0001), indicating that patients had significantly lower levels of explicit adaptive salience. Patients and healthy controls also did not differ on the number of errors they made or on the amount of money won.

3.2.1.2 Cross-sectional comparisons of salience attribution scores in patients and healthy controls at four-week follow up

Table 16 provides an overview of follow up SAT scores for patients and healthy controls (after four weeks).

Again, I first investigated whether the participants as a whole were able to use reward associations to guide how they responded (comparing responses on high-probability trials to those on low-probability trails). At four-week follow up, participants responded more quickly on high- relative to low-probability reinforced trials (t(39)=3.43, p=0.001). At follow up, the distribution of implicit adaptive salience measures were non-normal, so I conducted a one-sample Wilcoxon Signed-Rank Test against 0 to assess whether

patients and healthy controls exhibited significant implicit adaptive salience (significantly different to zero). As at baseline, healthy controls showed significant implicit adaptive salience at follow up ($p<0.0001$). However, in contrast to baseline, the patients now did too ($p=0.028$), indicating that both groups were able to differentiate between high- and low-probability cues.

Table 16: *Measures of salience attribution at four-week follow up*

Salience measure	Patients (n=20)	Healthy controls (n=21)	Test, sig.
RT adaptive salience (ms)	11.17 (31.62)	18.12 (22.84)	t(39)=-0.81, p=0.42
VAS adaptive salience (mm)	32.26 (30.89)	72.90 (25.75)	t(24)=-3.21, p=0.004*
RT aberrant salience (ms)	12.04 (11.57)	12.16 (7.74)	t(39)=-0.37, p=0.72
VAS aberrant salience (mm)	15.79 (13.21)	11.10 (17.34)	t(38)=1.70, p=0.097
Omission errors	0.25 (0.55)	0.29 (0.64)	Z<0.0001, p=1.00
Premature errors	1.10 (1.52)	1.52 (1.63)	Z=-1.02, p=0.31
Money won (£)	12.07 (6.08)	11.74 (5.86)	t(39)=0.17, p=0.86

RT=reaction time; ms=milliseconds; VAS=visual analogue scale; mm=millimetres; * p<0.05

Nevertheless, at follow up, patients still showed significantly lower explicit adaptive salience scores than healthy controls ($t(24)=-3.21$, $p=0.004$). There were no significant differences between the groups in any other salience score, including in errors made or money won (all n.s., $p>0.05$).

3.2.1.3 Longitudinal effects of four-week antipsychotic treatment on behavioural measures of salience attribution in FEP patients

Table 17 shows the longitudinal measures for patients and healthy controls who were scanned at two time points. I examined the effects of antipsychotic treatment on behavioural measures of salience attribution within the patient group by considering the

changes in these measures longitudinally. For comparison, I examined the stability of the measures in healthy controls across a similar period.

Table 17: *Measures of salience attribution over four weeks in patients and healthy controls scanned at two time points*

Salience measure	Baseline	Follow up	Test, sig.
Patients			
RT adaptive salience (ms)	11.18 (26.93)	11.17 (31.62)	t(19)=-0.71, p=0.49
VAS adaptive salience (mm)	21.66 (31.60)	32.26 (30.89)	t(18)=-1.36, p=0.19
RT aberrant salience (ms)	18.23 (15.50)	12.04 (11.57)	t(19)=1.55, p=0.14
VAS aberrant salience (mm)	13.13 (10.96)	15.79 (13.21)	t(18)=-0.91, p=0.37
Omission errors	0.50 (2.01)	0.25 (0.55)	Z=-0.14, p=0.89
Premature errors	2.50 (2.91)	1.10 (1.52)	Z=-2.50, p=0.012*
Money won (£)	10.15 (4.50)	12.07 (6.08)	Z=-0.67, p=0.50
Healthy controls			
RT adaptive salience (ms)	16.24 (25.74)	18.12 (22.84)	t(20)=-0.59, p=0.56
VAS adaptive salience (mm)	56.35 (33.36)	72.90 (25.75)	t(20)=-1.40, p=0.18
RT aberrant salience (ms)	14.35 (11.15)	12.16 (7.74)	t(20)=0.76, p=0.45
VAS aberrant salience (mm)	10.95 (9.71)	11.10 (17.34)	t(20)=0.56, p=0.58
Omission errors	0.25 (0.55)	0.29 (0.64)	Z=-0.18, p=0.86
Premature errors	1.45 (1.79)	1.52 (1.63)	Z=-0.57, p=0.57
Money won (£)	11.17 (5.60)	11.74 (5.86)	Z=-0.15, p=0.88

RT=reaction time; ms=milliseconds; VAS=visual analogue scale; mm=millimetres; * p<0.05

When baseline and follow-up scores were compared in patients, there was a significant decrease in the number of premature errors committed after treatment (Z=-2.50, p=0.012). There were no significant differences in any other measures. There were no significant differences between baseline and follow up scores in healthy controls, including errors and money won (all n.s., p>0.05).

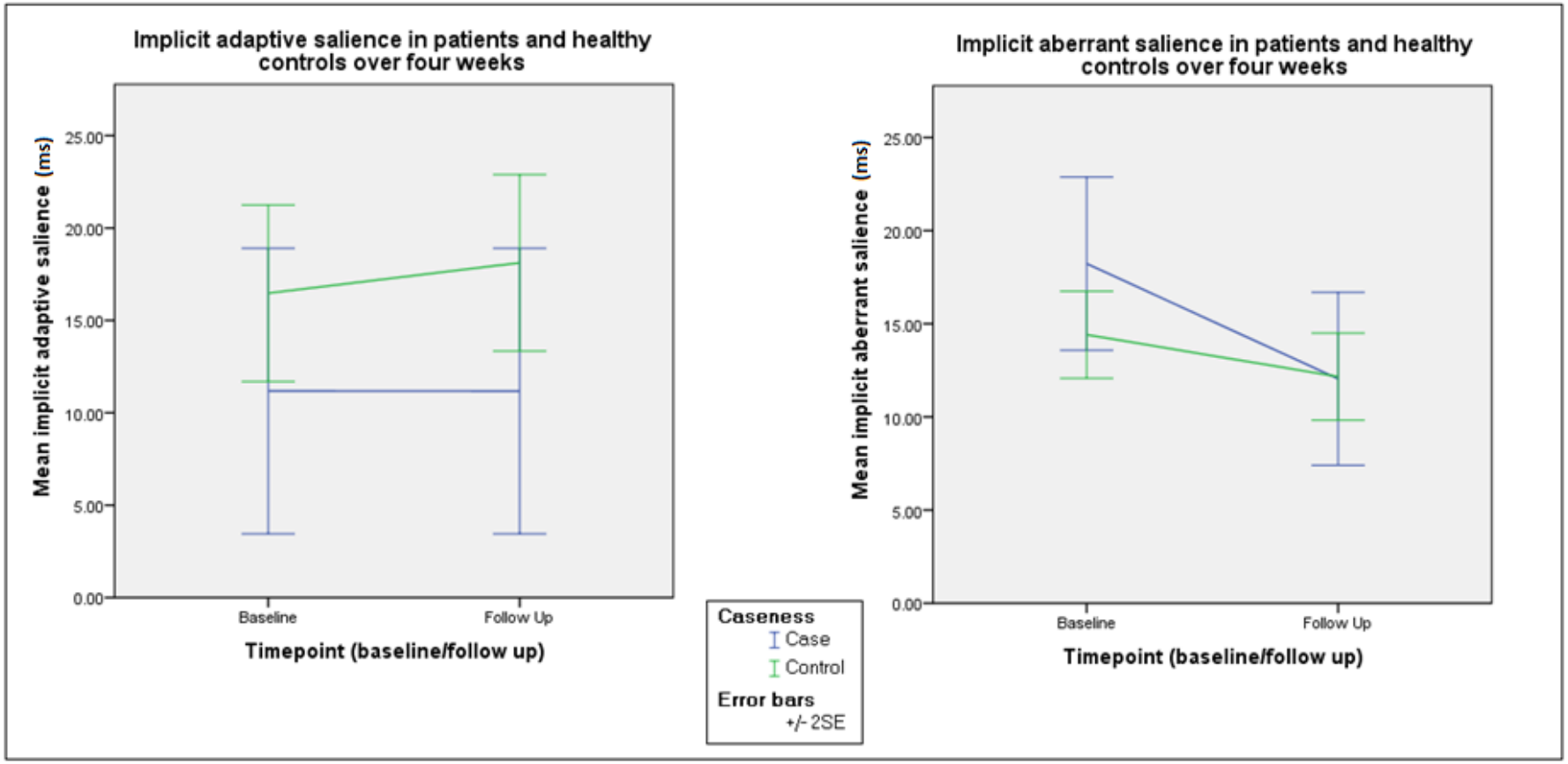

Figure 8: *Longitudinal changes in implicit adaptive and aberrant salience over four weeks, in patients and healthy controls*

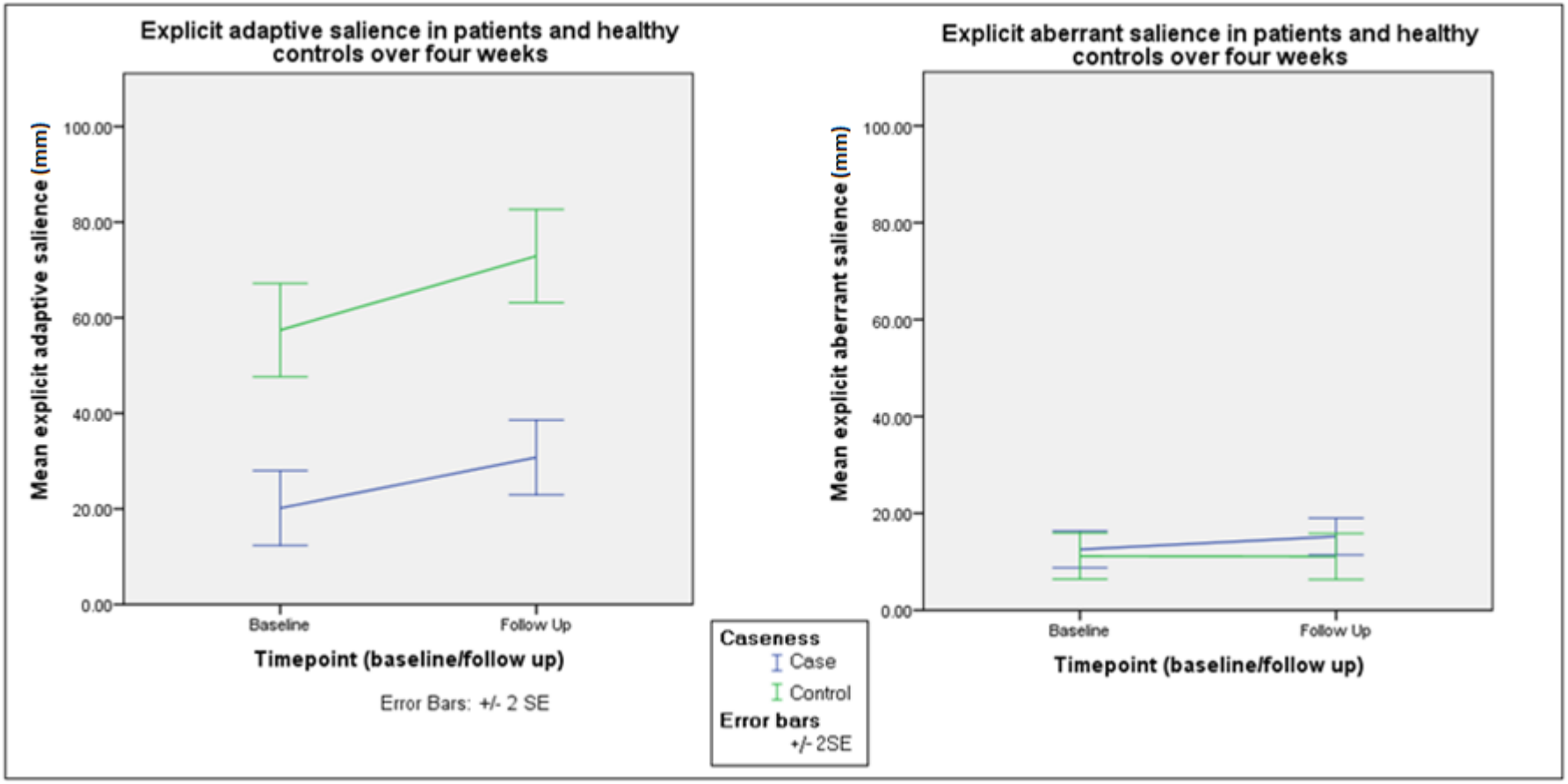

Figure 9: *Longitudinal changes in explicit adaptive and aberrant salience over four weeks, in patients and healthy controls*

3.2.2 Salience attribution measures in responders and non-responders

In these sections, I present the salience attribution scores for patients in relation to response to treatment at four and 12 weeks, to assess the associations of these variables with short- and longer-term treatment response.

3.2.2.1 Treatment response at four weeks

To investigate the relationship between treatment response and measures of salience attribution, I carried out cross-sectional and longitudinal analyses of these measures to compare responders and non-responders (and healthy controls). I also assessed whether there was a relationship between baseline and longitudinal salience attribution measures and continuous measures of response (percent change in PANSS scores).

3.2.2.1.1 Cross-sectional comparisons of baseline salience attribution in four-week responders and non-responders

a) Four-week responders versus non-responders

I first assessed whether there were any baseline differences between four-week responders and non-responders. Table 18 provides salience measures for responders and non-responders at baseline. These data were investigated to assess whether salience attribution processing at baseline differed in patients who were categorised as responders at four weeks compared with non-responders.

At baseline, responders had significantly higher implicit adaptive salience than non-responders ($t(16)=2.82$, $p=0.012$). There were no other differences between the two patient groups in measures of salience, including errors and money won (all n.s., $p>0.05$).

Table 18: *Measures of baseline salience attribution in four-week responders and non-responders*

Salience measure	Responders (n=14)	Non-responders (n=8)	Test, sig.
RT adaptive salience (ms)	17.25 (30.99)	-7.52 (8.30)	t(16)=2.82, p=0.012*
VAS adaptive salience (mm)	26.71 (35.32)	1.44 (15.20)	t(19)=1.76, p=0.10
RT aberrant salience (ms)	22.98 (17.45)	13.46 (13.23)	t(20)=1.47, p=0.16
VAS aberrant salience (mm)	10.07 (11.12)	14.31 (10.62)	t(20)=-1.05, p=0.31
Omission errors	0.71 (2.40)	0.13 (0.354)	Z=-0.17, p=0.92
Premature errors	2.43 (2.95)	2.50 (2.67)	Z=-0.28, p=0.82
Money won (£)	11.33 (3.52)	8.20 (5.04)	t(20)=1.71, p=0.10

RT=reaction time; ms=milliseconds; VAS=visual analogue scale; mm=millimetres; *p<0.05

b) Four-week responders versus healthy controls

I next assessed whether there were any baseline differences between four-week responders and healthy controls. Table 19 provides salience measures for responders and healthy controls at baseline.

Table 19: *Measures of baseline salience attribution in four-week responders and healthy controls*

Salience measure	Responders (n=14)	Healthy controls (n=21)	Test, sig.
RT adaptive salience (ms)	17.25 (30.99)	16.47 (25.11)	t(33)=0.081, p=0.94
VAS adaptive salience (mm)	26.71 (35.32)	57.40 (32.87)	t(33)=-2.63, p=0.013*
RT aberrant salience (ms)	22.98 (17.45)	14.41 (10.87)	t(33)=1.75, p=0.090
VAS aberrant salience (mm)	10.07 (11.12)	11.17 (9.51)	t(33)=-0.56, p=0.58
Omission errors	0.71 (2.40)	0.33 (0.66)	Z=-0.60, p=0.68
Premature errors	2.43 (2.95)	1.43 (1.75)	Z=-0.99, p=0.34
Money won (£)	11.33 (3.52)	11.16 (5.46)	t(33)=0.098, p=0.92

RT=reaction time; ms=milliseconds; VAS=visual analogue scale; mm=millimetres; *p<0.05

At baseline, four-week responders had significantly lower implicit adaptive salience than did healthy controls (t(33)=-2.63, p=0.013). There were no significant differences in any other measures of salience at baseline between responders and healthy controls.

c) Four-week non-responders versus healthy controls

Lastly, I assessed whether there were baseline differences between four-week non-responders and healthy controls. Table 20 provides salience measures for non-responders and healthy controls at baseline.

Table 20: *Measures of baseline salience attribution in 4-week non-responders and healthy controls*

Salience measure	Non-responders (n=8)	Healthy controls (n=21)	Test, sig.
RT adaptive salience (ms)	-7.52 (8.30)	16.47 (25.11)	t(27)=-3.86, p=0.001*
VAS adaptive salience (mm)	1.44 (15.20)	57.40 (32.87)	t(27)=-4.41, p<0.0001*
RT aberrant salience (ms)	13.46 (13.23)	14.41 (10.87)	t(27)=-0.29, p=0.77
VAS aberrant salience (mm)	14.31 (10.62)	11.17 (9.51)	t(27)=0.71, p=0.48
Omission errors	0.13 (0.354)	0.33 (0.66)	Z=-0.73, p=0.62
Premature errors	2.50 (2.67)	1.43 (1.75)	Z=-1.20, p=0.26
Money won (£)	8.20 (5.04)	11.16 (5.46)	t(27)=-1.33, p=0.20

RT=reaction time; ms=milliseconds; VAS=visual analogue scale; mm=millimetres; *p<0.05

At baseline, four-week non-responders had significantly lower levels of both implicit and explicit adaptive salience than did healthy controls (t(27)=-3.86, p=0.001 and t(27)=-4.41, p<0.0001, respectively). There were no significant differences between the groups on aberrant salience scores, errors or money won at baseline.

3.2.2.1.2 Cross-sectional comparisons of salience attribution in four-week responders and non-responders at four-week follow up

a) Four-week responders versus non-responders

I first assessed whether there were differences between four-week responders and non-responders at follow up after four weeks of treatment. Table 21 provides salience measures for responders and non-responders at baseline.

Table 21: *Measures of follow up salience attribution in four-week responders and non-responders*

Salience measure	Responders (n=14)	Non-responders (n=8)	Test, sig.
RT adaptive salience (ms)	17.30 (25.58)	1.98 (39.03)	t(18)=1.065, p=0.30
VAS adaptive salience (mm)	32.46 (28.94)	31.93 (36.44)	t(17)=0.035, p=0.97
RT aberrant salience (ms)	7.16 (4.63)	19.37 (15.08)	t(18)=-2.78, p=0.013*
VAS aberrant salience (mm)	18.46 (15.12)	11.21 (8.12)	t(17)=1.011, p=0.33
Omission errors	0.33 (0.65)	0.13 (0.35)	Z=-0.72, p=0.62
Premature errors	1.17 (1.75)	1.00 (1.20)	Z=-0.083, p=0.97
Money won (£)	11.12 (3.66)	13.50 (8.69)	t(18)=-0.85, p=0.41

RT=reaction time; ms=milliseconds; VAS=visual analogue scale; mm=millimetres; *p<0.05

After four weeks of treatment, there was no longer a significant difference between responders and non-responders in adaptive salience (t(18)=1.065, p=0.30), although adaptive salience in responders was still higher than that of non-responders (mean 17.3ms versus 1.98ms). However, responders after treatment showed significantly lower implicit aberrant salience than did non-responders (t(18)=-2.77, p=0.013). There were no other differences between the two patient groups in measures of salience, including errors and money won (all n.s., p>0.05).

b) Four-week responders versus healthy controls

I next assessed whether there were any differences between four-week responders and healthy controls at four-week follow up. Table 22 provides salience measures for responders and healthy controls at follow up.

Table 22: *Measures of follow up salience attribution in four-week responders and healthy controls*

Salience measure	Responders (n=14)	Healthy controls (n=21)	Test, sig.
RT adaptive salience (ms)	17.30 (25.58)	18.12 (22.84)	t(31)=-0.20, p=0.84
VAS adaptive salience (mm)	32.46 (28.94)	72.90 (25.75)	t(12.6)=-2.40, p<0.033*
RT aberrant salience (ms)	7.16 (4.63)	12.16 (7.74)	t(31)=-2.03, p=0.051
VAS aberrant salience (mm)	18.46 (15.12)	11.10 (17.34)	t(31)=1.73, p=0.093
Omission errors	0.33 (0.65)	0.29 (0.64)	Z=-0.34, p=0.81
Premature errors	1.17 (1.75)	1.52 (1.63)	Z=-0.88, p=0.41
Money won (£)	11.12 (3.66)	11.74 (5.86)	t(30.66)=-0.38, p=0.71

RT=reaction time; ms=milliseconds; VAS=visual analogue scale; mm=millimetres; *p<0.05

After four weeks of treatment, four-week responders still had lower implicit adaptive salience than healthy controls (t(12.6)=-2.40, p<0.033). There were no significant differences in any other measures of salience at follow up between responders and healthy controls.

c) Four-week non-responders versus healthy controls

Finally, I assessed whether there were any differences between four-week non-responders and healthy controls at four-week follow up. Table 23 provides salience measures for non-responders and healthy controls at follow up.

At follow up, four-week non-responders still had lower implicit adaptive salience scores than did healthy controls but this was no longer significant (t(27)=-1.39, p=0.18). However, explicit adaptive salience scores remained significantly lower in non-responders than in healthy controls (t(27)=-3.29, p=0.003). There were no significant differences between the groups on aberrant salience scores, errors or money won at follow up.

Table 23: *Measures of follow up salience attribution in four-week non-responders and healthy controls*

Salience measure	Non-responders (n=8)	Healthy controls (n=21)	Test, sig.
RT adaptive salience (ms)	1.98 (39.03)	18.12 (22.84)	t(27)=-1.39, p=0.18
VAS adaptive salience (mm)	31.93 (36.44)	72.90 (25.75)	t(27)=-3.29, p=0.003*
RT aberrant salience (ms)	19.37 (15.08)	12.16 (7.74)	t(27)=1.53, p=0.14
VAS aberrant salience (mm)	11.21 (8.12)	11.10 (17.34)	t(26)=0.78, p=0.45
Omission errors	0.13 (0.35)	0.29 (0.64)	Z=-0.48, p=0.76
Premature errors	1.00 (1.20)	1.52 (1.63)	Z=-0.76, p=0.49
Money won (£)	13.50 (8.69)	11.74 (5.86)	t(27)=0.63, p=0.54

RT=reaction time; ms=milliseconds; VAS=visual analogue scale; mm=millimetres

3.2.2.1.3 Longitudinal effects of four-week antipsychotic treatment on clinical measures in four-week responders

To assess whether there were changes in any measures of salience within four-week responders during four weeks of treatment, I compared baseline and follow up measures in this group (Table 24 and Figure 10).

In four-week responders there was a significant decrease in implicit aberrant salience (t(11)=3.095, p=0.01) and the number of premature errors (Z=-2.13, p=0.033). There were no significant changes in any other salience measures or in the amount of money won by responders.

3.2.2.1.4 Longitudinal effects of four-week antipsychotic treatment on salience measures in four-week non-responders

To assess whether there were changes in any measures of salience within four-week non-responders during four weeks of treatment, I compared baseline and follow up measures in this group (Table 24 and Figure 11).

In four-week non-responders there was a significant increase in explicit adaptive salience (t(6)=-2.73, p-0.034) but no changes in any other measure of salience, errors or money won. This suggests that following treatment non-responders were better able to differentiate between high and low probability cues but that this learning was not reflected in their reaction times.

Table 24: *Measures of baseline and follow up salience attribution in four-week responders and non-responders*

Salience measure	Baseline	Follow up	Test, sig.
Responders (n=14)			
RT adaptive salience (ms)	17.25 (30.99)	17.30 (25.58)	t(11)=-0.77, p=0.46
VAS adaptive salience (mm)	26.71 (35.32)	32.46 (28.94)	t(11)=0.066, p=0.95
RT aberrant salience (ms)	22.98 (17.45)	7.16 (4.63)	t(11)=3.10, p=0.01*
VAS aberrant salience (mm)	10.07 (11.12)	18.46 (15.12)	t(11)=-1.42, p=0.18
Omission errors	0.71 (2.40)	0.33 (0.65)	Z=0.00, p=1.00
Premature errors	2.43 (2.95)	1.17 (1.75)	Z=-2.13, p=0.033*
Money won (£)	11.33 (3.52)	11.12 (3.66)	t(11)=0.22, p=0.83
Non-responders (n=8)			
RT adaptive salience (ms)	-7.52 (8.30)	1.98 (39.03)	t(7)=-0.64, p=0.54
VAS adaptive salience (mm)	1.44 (15.20)	31.93 (36.44)	t(7)=-2.73, p=0.034*
RT aberrant salience (ms)	13.46 (13.23)	19.37 (15.08)	t(7)=-0.90, p=0.40
VAS aberrant salience (mm)	14.31 (10.62)	11.21 (8.12)	t(6)=0.89, p=0.41
Omission errors	0.13 (0.354)	0.13 (0.35)	Z=-0.00, p=1.00
Premature errors	2.50 (2.67)	1.00 (1.20)	Z=-1.28, p=0.20
Money won (£)	8.20 (5.04)	13.50 (8.69)	t(7)=-1.70, p=0.13

RT=reaction time; ms=milliseconds; VAS=visual analogue scale; mm=millimetres; *p<0.05

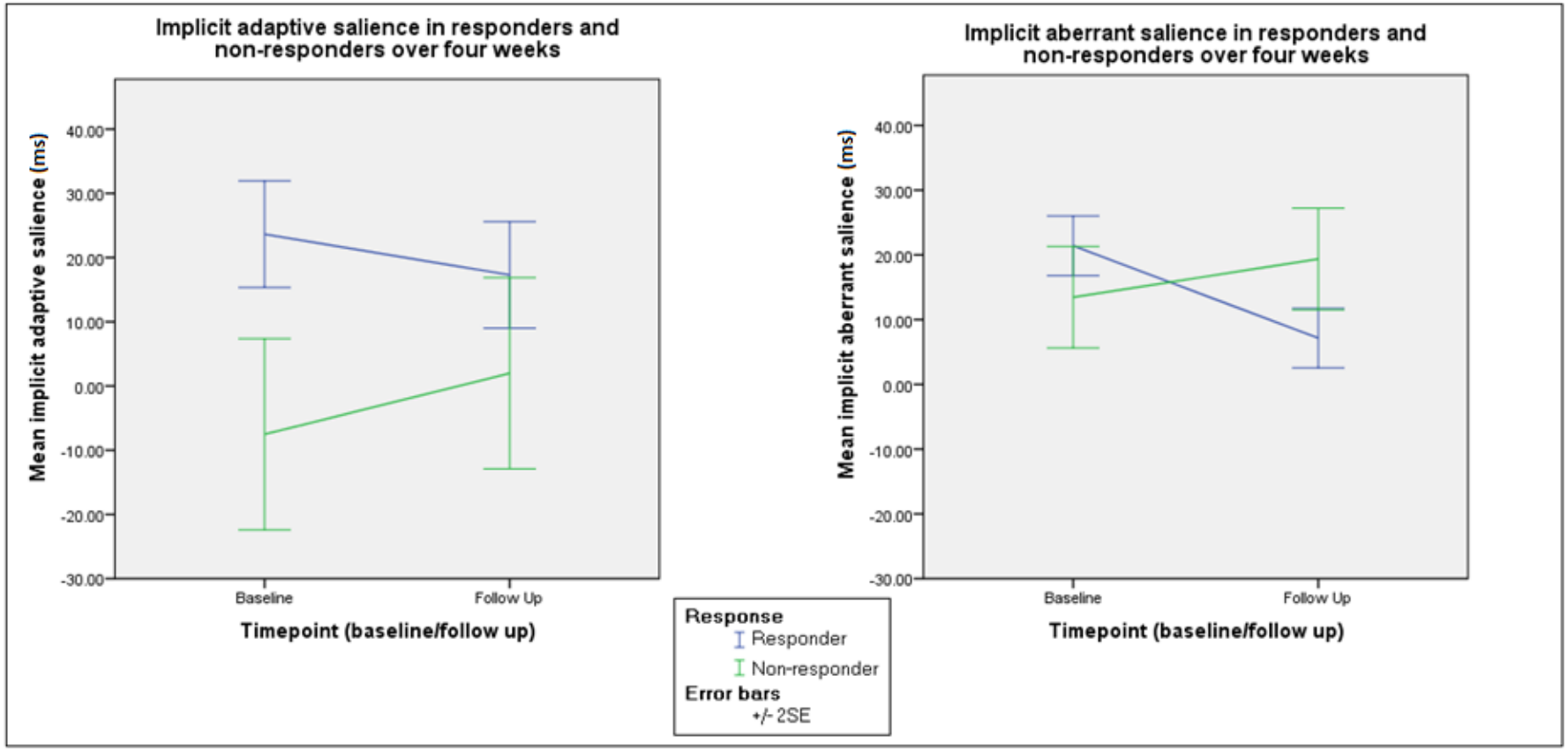

Figure 10: *Implicit adaptive and aberrant salience in responders and non-responders over four weeks*

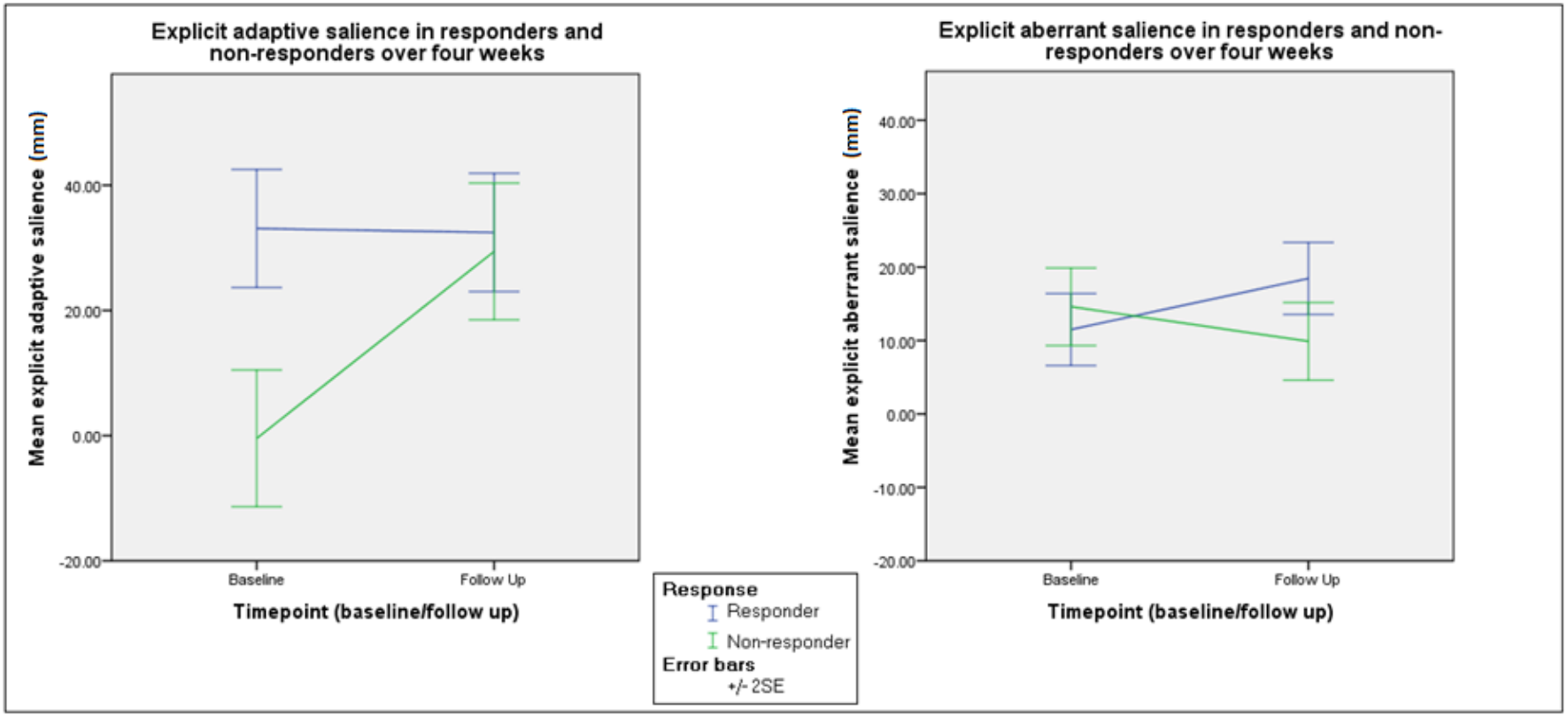

Figure 11: *Explicit adaptive and aberrant salience in responders and non-responders over four weeks*

3.2.2.1.5 Associations between salience attribution measures and a continuous measure of treatment response at four weeks

As there were relatively few non-responders in our sample, I also assessed a continuous measure of treatment response (at four weeks) in the form of percentage change scores, using the same methods as described for the clinical measures (see Methods, page 101). I investigated the relationships between baseline and four-week follow up measures of salience and percentage change in PANSS score using Spearman's Rho.

There was no relationship between baseline implicit adaptive salience or implicit/explicit aberrant salience and percentage change in any of the subscales or the total PANSS scores (all n.s., $p>0.05$). Baseline explicit adaptive salience was positively correlated with percentage change on all subscales and total PANSS scores (positive: $R=0.44$, $p=0.044$; negative: $R=0.56$, $p=0.008$; general psychopathology: $R=0.46$, $p=0.036$; and total: $R=0.56$, $p=0.008$). This was such that higher scores of explicit adaptive salience before treatment were related to bigger changes in all symptom scores following four weeks of treatment.

Four-week follow up implicit/explicit adaptive salience and explicit aberrant salience scores were not related to percent change in any of the subscales or the total PANSS scores (all n.s., $p>0.05$). Follow up implicit aberrant salience scores were significantly negatively correlated with percent change in positive, general psychopathology, and total PANSS scores ($R=-0.51$, $p=0.024$; $R=-0.57$, $p=0.011$; and $R=-0.58$, $p=0.010$, respectively) but not negative PANSS scores (n.s., $p>0.05$).

Errors made and money won at either baseline or follow up were not significantly correlated with percent change in any of the subscales or total PANSS scores (all n.s., $p>0.05$).

3.2.2.2 Treatment response at 12 weeks

To investigate the relationship between longer-term treatment response and measures of salience attribution, I carried out cross-sectional and longitudinal analyses of these measures to compare responders and non-responders defined at 12 weeks (and healthy controls).

3.2.2.2.1 Cross-sectional comparisons of baseline salience attribution in 12-week responders and non-responders

a) Twelve-week responders versus non-responders

I first assessed whether there were any baseline differences between 12-week responders and non-responders. Table 25 provides salience measures for 12-week responders and non-responders at baseline.

Table 25: *Measures of baseline salience attribution in 12-week responders and non-responders*

Salience measure	Responders (n=10)	Non-responders (n=8)	Test, sig.
RT adaptive salience (ms)	11.54 (27.25)	6.67 (34.00)	Z=-0.32, p=0.80
VAS adaptive salience (mm)	15.56 (27.71)	6.07 (25.73)	Z=-1.42, p=0.16
RT aberrant salience (ms)	28.53 (19.94)	9.37 (4.61)	t(14)=2.58, p=0.022*
VAS aberrant salience (mm)	11.25 (11.78)	14.57 (11.79)	Z=-0.58, p=0.57
Omission errors	0.13 (0.35)	0.00 (0.00)	Z=-1.00, p=0.72
Premature errors	2.50 (3.74)	2.71 (2.81)	Z=-0.60, p=0.57
Money won (£)	12.80 (4.49)	7.51 (3.55)	t(14)=2.74, p=0.016*

RT=reaction time; ms=milliseconds; VAS=visual analogue scale; mm=millimetres; *p<0.05

At baseline, 12-week responders had significantly higher implicit aberrant salience than did later non-responders (t(14)=2.58, p=0.022). Twelve-week responders also won more money than non-responders (t(14)=2.74, p=0.016). There were no other

differences between the two patient groups in measures of salience, including errors committed (all n.s., p>0.05).

b) Twelve-week responders versus healthy controls

I next assessed whether there were any baseline differences between 12-week responders and healthy controls. Table 26 provides salience measures for 12-week responders and healthy controls at baseline.

Table 26: *Measures of baseline salience attribution in 12-week responders and healthy controls*

Salience measure	Responders (n=10)	Healthy controls (n=21)	Test, sig.
RT adaptive salience (ms)	11.54 (27.25)	16.47 (25.11)	t(29)=-1.14, p=0.26
VAS adaptive salience (mm)	15.56 (27.71)	57.40 (32.87)	t(29)=-3.90, p=0.001*
RT aberrant salience (ms)	28.53 (19.94)	14.41 (10.87)	t(11.67)=2.22, p=0.046*
VAS aberrant salience (mm)	11.25 (11.78)	11.17 (9.51)	Z=-0.91, p=0.37
Omission errors	0.13 (0.35)	0.33 (0.66)	Z=-0.35, p=0.82
Premature errors	2.50 (3.74)	1.43 (1.75)	Z=-0.62, p=0.57
Money won (£)	12.80 (4.49)	11.16 (5.46)	t(29)=0.61, p=0.55

RT=reaction time; ms=milliseconds; VAS=visual analogue scale; mm=millimetres; *p<0.05

At baseline, 12-week responders had significantly lower explicit adaptive salience than did healthy controls (t(29)=-3.90, p=0.001). There were no significant differences in any other measures of salience at baseline between responders and healthy controls.

c) Twelve-week non-responders versus healthy controls

Lastly, I assessed whether there were any baseline differences between 12-week non-responders and healthy controls. Table 27 provides salience measures for 12-week non-responders and healthy controls at baseline.

Table 27: *Measures of baseline salience attribution in 12-week non-responders and healthy controls*

Salience measure	Non-responders (n=8)	Healthy controls (n=21)	Test, sig.
RT adaptive salience (ms)	6.67 (34.00)	16.47 (25.11)	Z=-1.90, p=0.059
VAS adaptive salience (mm)	6.07 (25.73)	57.40 (32.87)	Z=-3.20, p=0.001*
RT aberrant salience (ms)	9.37 (4.61)	14.41 (10.87)	t(27)=-1.13, p=0.27
VAS aberrant salience (mm)	14.57 (11.79)	11.17 (9.51)	Z=-.0.29, p=0.79
Omission errors	0.00 (0.00)	0.33 (0.66)	Z=-1.48, p=0.35
Premature errors	2.71 (2.81)	1.43 (1.75)	Z=-1.20, p=0.26
Money won (£)	7.51 (3.55)	11.16 (5.46)	t(270=-1.82, p=0.080

RT=reaction time; ms=milliseconds; VAS=visual analogue scale; mm=millimetres; *p<0.05

At baseline, 12-week non-responders had significantly lower levels of explicit adaptive salience than healthy controls (Z=-3.20, p=0.001). There were no significant differences between the groups on implicit adaptive salience, aberrant salience scores, errors or money won at baseline.

3.2.2.2.2 Cross-sectional comparisons of follow up salience attribution in 12-week responders and non-responders

a) Twelve-week responders versus non-responders

I first assessed whether there were any follow up differences (after four weeks of treatment) between 12-week responders and non-responders. Table 28 provides salience measures for responders and non-responders at baseline.

At follow up, 12-week responders and non-responders still differed on implicit aberrant salience scores (t(14)=-2.42, p=0.030) but there was no longer a significant difference the groups in money won (t(14)=-1.20, p=0.25). There were no other significant differences in adaptive salience, explicit aberrant salience or errors made. This suggests that despite treatment non-responders still had higher levels of aberrant salience than did responders.

Table 28: *Measures of follow up salience attribution in 12-week responders and non-responders*

Salience measure	Responders (n=8)	Non-responders (n=8)	Test, sig.
RT adaptive salience (ms)	21.92 (28.25)	5.31 (42.67)	t(14)=1.06, p=0.31
VAS adaptive salience (mm)	26.44 (26.95)	34.79 (38.80)	Z=-0.58, p=0.61
RT aberrant salience (ms)	6.45 (4.65)	19.52 (15.97)	t(14)=-2.42, p=0.030*
VAS aberrant salience (mm)	15.31 (11.84)	9.07 (2.04)	t(13)=1.28, p=0.22
Omission errors	0.00 (0.00)	0.00 (0.00)	-
Premature errors	1.13 (2.10)	0.71 (0.95)	Z=-1.00, p=0.72
Money won (£)	9.91 (3.14)	15.38 (8.26)	t(14)=-1.20, p=0.25

RT=reaction time; ms=milliseconds; VAS=visual analogue scale; mm=millimetres; *p<0.05

b) Twelve-week responders versus healthy controls

I next assessed whether there were any follow up differences between 12-week responders and healthy controls. Table 29 provides salience measures for responders and healthy controls at follow up.

Table 29: *Measures of follow up salience attribution in 12-week responders and healthy controls*

Salience measure	Responders (n=8)	Healthy controls (n=21)	Test, sig.
RT adaptive salience (ms)	21.92 (28.25)	18.12 (22.84)	t(27)=0.38, p=0.71
VAS adaptive salience (mm)	26.44 (26.95)	72.90 (25.75)	t(27)=-4.29, p<0.0001*
RT aberrant salience (ms)	6.45 (4.65)	12.16 (7.74)	t(27)=-1.95, p=0.062
VAS aberrant salience (mm)	15.31 (11.84)	11.10 (17.34)	t(27)=0.63, p=0.53
Omission errors	0.00 (0.00)	0.29 (0.64)	Z=-1.30, p=0.46
Premature errors	1.13 (2.10)	1.52 (1.63)	Z=-1.12, p=0.30
Money won (£)	9.91 (3.14)	11.74 (5.86)	t(23.44)=-1.083, p=0.29

RT=reaction time; ms=milliseconds; VAS=visual analogue scale; mm=millimetres; *p<0.05

After four weeks of treatment, 12-week responders still had lower explicit adaptive salience than healthy controls (t(27)=-4.29, p<0.0001). There were no significant differences in any other measures of salience at follow up between 12-week responders and healthy controls.

c) Twelve-week non-responders versus healthy controls

Finally, I assessed whether there were any follow up differences between 12-week non-responders and healthy controls. Table 30 provides salience measures for non-responders and healthy controls at follow up.

Table 30: *Measures of follow up salience attribution in 12-week non-responders and healthy controls*

Salience measure	Non-responders (n=8)	Healthy controls (n=21)	Test, sig.
RT adaptive salience (ms)	5.31 (42.67)	18.12 (22.84)	t(27)=-1.23, p=0.23
VAS adaptive salience (mm)	34.79 (38.80)	72.90 (25.75)	Z=-2.39, p=0.014*
RT aberrant salience (ms)	19.52 (15.97)	12.16 (7.74)	t(27)=1.80, p=0.083
VAS aberrant salience (mm)	9.07 (2.04)	11.10 (17.34)	t(26)=-0.30, p=0.77
Omission errors	0.00 (0.00)	0.29 (0.64)	t(27)=-0.66, p=0.51
Premature errors	0.71 (0.95)	1.52 (1.63)	Z=-0.76, p=0.49
Money won (£)	15.38 (8.26)	11.74 (5.86)	t(27)=0.76, p=0.45

RT=reaction time; ms=milliseconds; VAS=visual analogue scale; mm=millimetres; *p<0.05

After four weeks of treatment, 12-week non-responders still had significantly lower explicit adaptive salience scores than healthy controls (Z=-2.39, p=0.014). There were no significant differences in any other measures of salience at follow up between 12-week non-responders and healthy controls.

3.2.2.2.3 Longitudinal effects of four-week antipsychotic treatment on clinical measures in 12-week responders

To assess whether there were changes in any measures of salience within 12-week responders during four weeks of treatment, I compared baseline and follow up measures in this group (Table 31).

In 12-week responders there was a significant decrease in implicit aberrant salience after four weeks of treatment (t(7)=3.37, p=0.012). There were no significant changes in any other salience measures, errors made or the amount of money won by 12-week responders. This suggests that in responders four weeks of antipsychotic treatment led to decreased levels of aberrant salience.

Table 31: *Measures of salience attribution at baseline and follow up in 12-week responders and non-responders*

Salience measure	**Baseline**	**Follow up**	**Test, sig.**
Responders	(n=10)	(n=8)	
RT adaptive salience (ms)	11.54 (27.25)	21.92 (28.25)	t(7)=-1.48, p=0.18
VAS adaptive salience (mm)	15.56 (27.71)	26.44 (26.95)	t(7)=-1.23, p=0.26
RT aberrant salience (ms)	28.53 (19.94)	6.45 (4.65)	t(7)=3.37, p=0.012*
VAS aberrant salience (mm)	11.25 (11.78)	15.31 (11.84)	Z=-0.70, p=0.48
Omission errors	0.13 (0.35)	0.00 (0.00)	Z=-1.00, p=0.32
Premature errors	2.50 (3.74)	1.13 (2.10)	Z=-1.83, p=0.068
Money won (£)	12.80 (4.49)	9.91 (3.14)	t(7)=2.040, p=0.081
Non-responders	(n=8)	(n=8)	
RT adaptive salience (ms)	6.67 (34.00)	5.31 (42.67)	Z=-0.56, p=0.58
VAS adaptive salience (mm)	6.07 (25.73)	34.79 (38.80)	Z=-2.37, 0.018*
RT aberrant salience (ms)	9.37 (4.61)	19.52 (15.97)	t(7)=-1.87, p=0.10
VAS aberrant salience (mm)	14.57 (11.79)	9.07 (2.04)	t(6)=1.14, p=0.30
Omission errors	0.00 (0.00)	0.00 (0.00)	t(7)=-1.00, p=0.35
Premature errors	2.71 (2.81)	0.71 (0.95)	Z=-1.28, p=0.201
Money won (£)	7.51 (3.55)	15.38 (8.26)	t(7)=-2.35, p=0.051

RT=reaction time; ms=milliseconds; VAS=visual analogue scale; mm=millimetres; *p<0.05

3.2.2.2.4 Longitudinal effects of four-week antipsychotic treatment on clinical measures in 12-week non-responders

To assess whether there were changes in any measures of salience within 12-week non-responders during four weeks of treatment, I compared baseline and follow up measures in this group (Table 31).

In 12-week non-responders there was a significant increase after four weeks of treatment in explicit adaptive salience (Z=-2.37, 0.018) but no changes in any other measure of salience, errors or money won. This suggests that whilst treatment does not decrease levels of aberrant salience in non-responders, it does increase their ability to differentiate between high- and low-probability cues at an explicit level.

3.2.3 Associations between salience attribution measures and delusions

Given that Roiser and colleagues (2009) reported a relationship between delusions and aberrant salience in treated patients with FEP, I also investigated whether there were differences in salience measures between patients with delusions and those without delusions at both baseline and four-week follow up. There was a trend for those with delusions at follow up to have higher implicit aberrant salience at follow up ($t(18)=2.08$, $p=0.052$), but this did not reach significance. I also found that patients without delusions at follow up had significantly higher baseline implicit adaptive salience than patients who were delusional at follow up ($t(18.14)=-2.80$, $p=0.012$).

3.2.4 Neural activation associated with salience attribution in patients and healthy controls

Here, I present the imaging data showing activation associated with measures of salience attribution in both patients and healthy controls. These analyses try to identify abnormalities in salience activation in patients with FEP. They also investigate the effects of antipsychotic treatment on neural activation in a group of previously

untreated patients with FEP. I present both cross-sectional and longitudinal analyses of neural activation in these groups.

3.2.4.1 Neural activation associated with salience attribution at baseline

Initially, random-effects group-level analyses, using a one-sample t-test in patients and healthy controls separately, were used to investigate group-level activation at baseline associated with each of the contrasts described in Methods (page 108): adaptive salience, aberrant salience, and outcome (response to parametrically mediated reward in the form of money from 0p – 100p, indicated on the screen). This analysis investigates the brain regions activated in association with salience processing in patients and healthy controls.

a) Healthy controls

Significant clusters of activation associated with adaptive salience, aberrant salience, and outcome in healthy controls at baseline are shown in Table 32 and Figure 12.

Table 32: *Areas of increased neural activation associated with measures of salience and trial outcomes in healthy controls at baseline*

Coordinates are shown in MNI space. P values have been FWE-corrected for multiple comparisons across the whole brain. Values for cluster-level significance are reported.

Brain area	L/R	x	y	z	t	K_E	P value
Adaptive salience (increases)							
Superior temporal gyrus	L	-54	-18	0	6.67	1173	<0.0001
	R	68	-30	12	4.65	1120	<0.0001
Adaptive salience (decreases)							
Middle temporal gyrus	R	56	-58	16	5.08	533	0.009
Outcome (increases)							
Middle frontal gyrus	R	42	42	10	6.11	597	0.003
	L	-6	62	12	5.25	1037	<0.0001

At baseline, in healthy controls adaptive salience was associated with activation in two clusters (Table 32), in the superior temporal gyrus, bilaterally, and with a cluster of decreased activation in the posterior part of the right middle temporal gyrus, extending into the angular gyrus (Fig 12a). The outcome of trials (Table 32) was associated with activation in the right middle frontal gyrus and the left medial frontal gyrus (Fig 12b).

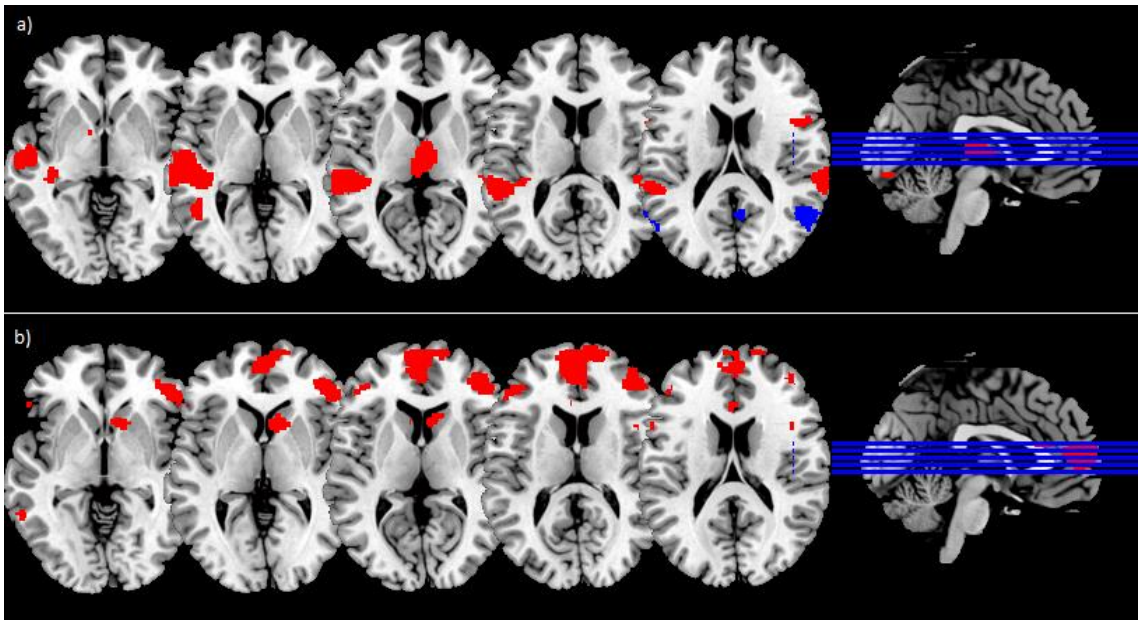

Figure 12: *Areas of increased (red) and decreased (blue) neural activation associated with a) adaptive salience and b) trial outcomes in healthy controls at baseline*

a) Healthy controls showed increased activation in superior temporal regions and decreased activation in middle temporal gyrus during adaptive salience processing at baseline; b) when presented with the outcome of trials, there was increased activation in frontal regions of healthy controls at baseline.

b) Patients

Significant clusters of activation associated with adaptive salience, aberrant salience, and outcome in patients at baseline are shown in Table 33 and Figure 13.

Table 33: *Areas of increased neural activation associated with measures of salience and trial outcomes in patients at baseline.*

Coordinates are shown in MNI space. P values have been FWE-corrected for multiple comparisons across the whole brain. Values for cluster-level significance are reported.

Brain area	L/R	x	y	z	t	K_E	P value
Outcome (increases)							
Cingulate gyrus	L	-10	32	32	6.52	1007	<0.0001
Middle frontal gyrus	R	36	6	44	5.11	580	0.003
Precentral gyrus	L	-38	0	36	5.06	580	0.032
Inferior frontal gyrus	L	-46	22	-10	4.95	402	0.016

At baseline, aberrant salience was not associated with any regions of significantly increased or decreased activation associated with aberrant salience in patients. Similarly, adaptive salience was not associated with any regions of significantly increased or decreased activation.

In contrast, trial outcome in patients was associated with activation in four clusters (Table 33). The first was centred on the left cingulate, extending into the right medial frontal gyrus. The second was centred on the right middle frontal gyrus, extending into the right inferior frontal gyrus. The third was centred on the left precentral gyrus, extending into regions of the inferior frontal gyrus. The final cluster was centred on the left inferior frontal gyrus, extending into the middle temporal gyrus and temporal pole.

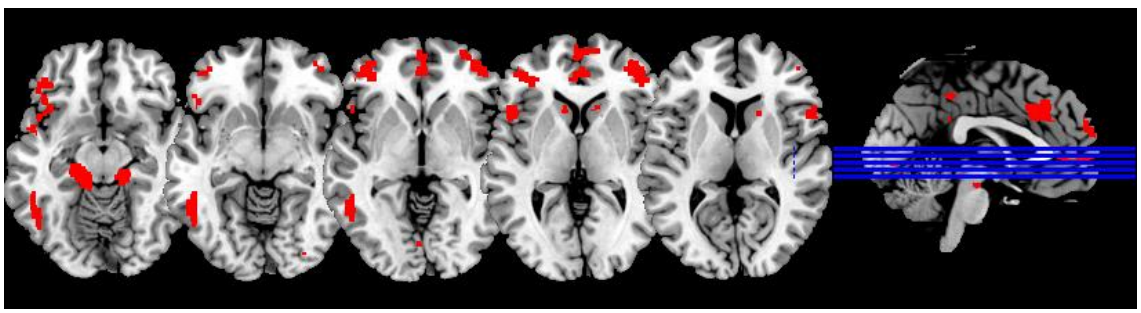

Figure 13: *Areas of increased activation associated with baseline outcomes in patients*

At baseline, when presented with the outcome of trials, there was increased activation in parietal, temporal, and frontal regions of patients.

3.2.4.2 Cross-sectional comparisons of salience activation in patients and healthy controls at baseline

I compared patients and healthy controls at baseline using an exploratory voxel-wide search (paired t-test) with $p<0.001$, uncorrected. Clusters identified were then explored for suprathreshold statistics accepted at $p<0.05$ (FWE-corrected). These analyses explored between-group differences in activation when comparing patients and healthy controls, whilst completing the SAT at baseline.

At baseline, there were no significant differences in activation between patients and healthy controls for adaptive salience, aberrant salience or outcome.

3.2.4.3 Neural activation associated with salience attribution at four-week follow up

Initially, random-effects group-level analyses, using a one-sample t-test in patients and healthy controls separately, were used to investigate group-level activation at follow up associated with each of the contrasts described in Methods (page 108): adaptive salience, aberrant salience, and outcome.

a) Healthy controls

Significant clusters of activation associated with adaptive salience, aberrant salience, and outcome in healthy controls at follow up are shown in Table 34 and Figure 14.

Table 34: *Areas of activation associated with measures of salience and trial outcomes in healthy controls at follow up*

Coordinates are shown in MNI space. P values have been FWE-corrected for multiple comparisons across the whole brain. Values for cluster-level significance are reported.

Brain area	L/R	x	y	z	t	K_E	P value
Adaptive salience (increases)							
Superior temporal gyrus	R	62	-34	6	8.88	2295	<0.0001
	L	-40	-38	8	6.29	1339	<0.0001
Inferior occipital gyrus	L	-36	-70	-6	6.91	980	<0.0001
Precentral gyrus	R	44	-2	48	5.38	915	<0.0001
Parahippocampal	L	-14	-30	-14	5.34	822	0.001
Outcome (increases)							
Inferior parietal lobe	R	46	-50	50	8.71	444	0.009
	L	-48	-40	50	5.22	526	0.004
Inferior temporal gyrus	L	-54	-54	-12	5.74	1985	<0.0001
Middle temporal gyrus	R	62	-50	-10	5.35	333	0.027

At follow up, in healthy controls there was increased activation associated with adaptive salience in five significant clusters (Table 34). There were two clusters of significant activation in the superior temporal gyrus, one in each hemisphere. There was a third cluster centred on the left inferior occipital lobe, extending into the left middle occipital gyrus. A fourth cluster centred on the right precentral gyrus of the frontal lobe, extending into the inferior frontal lobe. A final cluster centred on the left parahippocampal region, extending into the midbrain close to the substantia nigra. There were no regions of significantly decreased activation associated with adaptive salience in healthy controls at follow up. There were no regions of significantly increased or decreased activation associated with aberrant salience in healthy controls at follow up.

Several regions were activated in association with the outcome of trials (Table 34). Four clusters of significantly increased activation were found. There were two clusters

of significantly increased activation in the inferior parietal lobule, one in each hemisphere. There was also a cluster in the left inferior temporal gyrus, extending into the right vermis of the cerebellum. A further cluster was found in the right middle temporal gyrus including the fusiform gyrus and also extending into the right declive of the cerebellum.

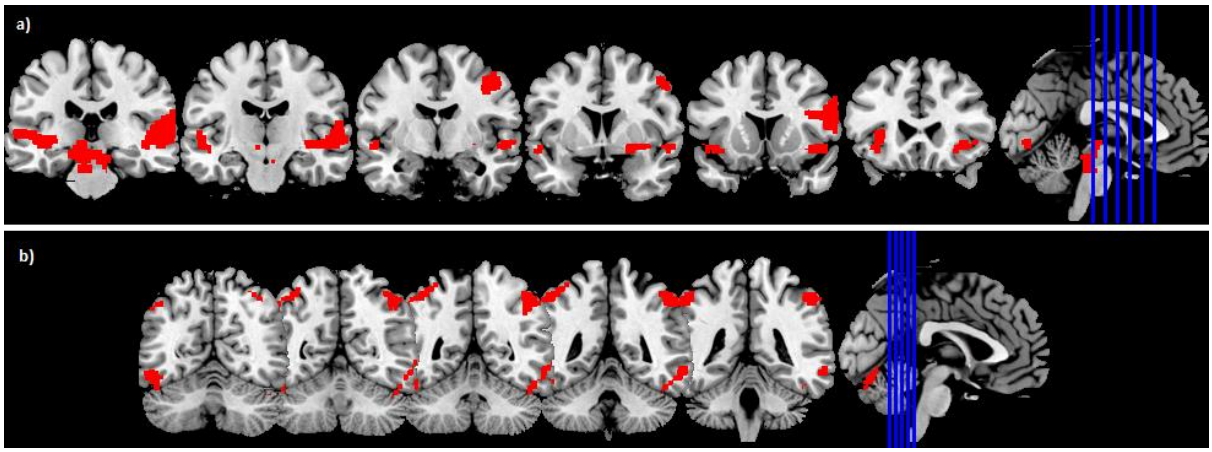

Figure 14: *Areas of activation associated with a) adaptive salience and b) trial outcomes in healthy controls at follow up*

At follow up, a) healthy controls showed increased activation in temporal, occipital and frontal regions during adaptive salience processing; b) when presented with the outcome of trials, there was increased activation in parietal and temporal regions of healthy controls.

b) Patients

Significant clusters of activation associated with adaptive salience, aberrant salience, and outcome in patients at follow up are shown in Table 35 and Figure 15.

Table 35: *Areas of increased neural activation associated with measures of salience and trial outcomes in patients at follow up*

Coordinates are shown in MNI space. P values have been FWE-corrected for multiple comparisons across the whole brain. Values for cluster-level significance are reported.

Brain area	L/R	x	y	z	t	K_E	P value
Adaptive salience (increases)							
Superior temporal gyrus	R	60	-24	8	5.90	581	0.011
	L	-42	-36	10	7.41	834	0.002
Outcome (increases)							
Superior temporal gyrus	R	58	-12	-12	7.55	1184	<0.0001
	L	-32	4	-16	6.39	967	<0.0001
Inferior temporal gyrus	R	54	-52	-16	6.14	323	0.046
	L	-56	-66	-10	6.76	519	0.009
Inferior parietal lobe	R	52	-46	50	7.03	692	0.002
Inferior frontal gyrus	R	44	48	4	6.08	418	0.02

At follow up, in patients there was increased activation associated with adaptive salience in two significant clusters (Table 35). These two clusters of significantly increased activation were centred in the superior temporal gyrus, one in each hemisphere, with activation on the left extending into the insula. There were no regions of significantly decreased activation associated with adaptive salience in patients at follow up. There were no regions of significantly increased or decreased activation associated with aberrant salience in patients at follow up.

Several regions were activated in association with the outcome of trials (Table 35). Six clusters of significantly increased activation were found in patients. There were two clusters of significantly increased activation in the superior temporal gyrus, one in each hemisphere. There were also two clusters, one in each hemisphere, of significantly increased activation in the inferior temporal gyrus, extending on both sides into middle temporal gyrus. There were further regions of activation in the right inferior parietal lobe

and right inferior frontal gyrus. There were no regions of significantly decreased activation associated with outcome in patients at follow up.

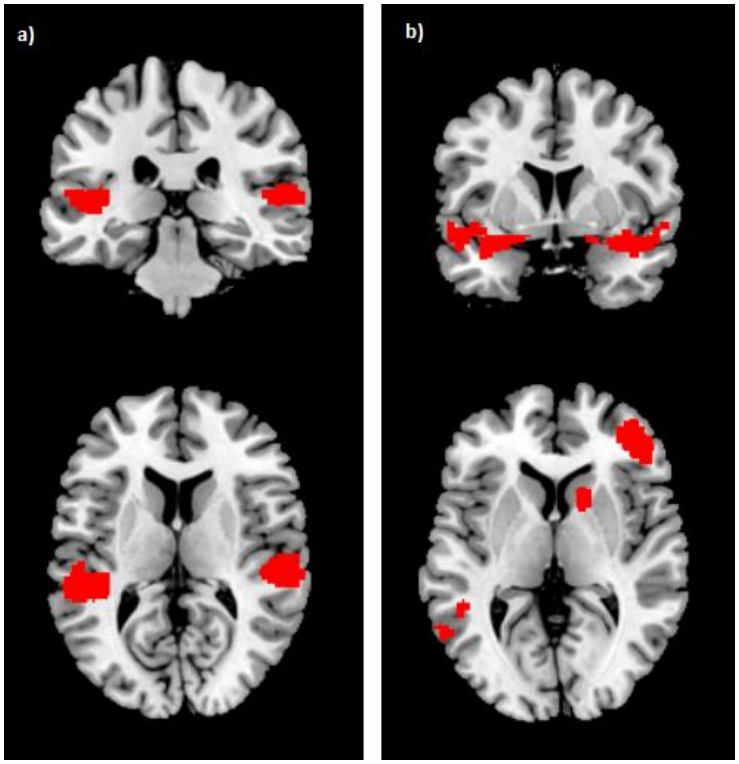

Figure 15: *Areas of activation associated with a) adaptive salience and b) trial outcomes in patients at follow up*

At follow up, a) patients showed increased activation bilaterally in temporal cortex during adaptive salience processing; b) when presented with the outcome of trials, there was increased activation in parietal, temporal, and frontal regions of patients.

3.2.4.4 Cross-sectional comparisons of salience activation in patients and healthy controls at four-week follow up

I compared patients and healthy controls at follow up using an exploratory voxel-wide search with $p<0.001$, uncorrected. Clusters identified were then explored for suprathreshold statistics accepted at $p<0.05$ (FWE-corrected). These analyses explored between-group differences in neural activation when comparing patients and healthy controls, whilst completing the SAT at follow up.

At follow up, there were no significant differences between patients and healthy controls for adaptive salience, aberrant salience or outcome.

3.2.4.5 Longitudinal effects of four-week antipsychotic treatment on neural activation underlying salience attribution

To explore the effects of antipsychotic medications on neural activation, changes from baseline to follow up (after four weeks of treatment) were identified using an exploratory voxel-wide search performed with $p<0.001$, uncorrected. Clusters identified were then explored for suprathreshold statistics accepted at $p<0.05$ and FWE corrected.

In patients, follow up scans, after four weeks of treatment, were compared with baseline scans, at which patients were antipsychotic-naïve/minimally treated, to identify any activation changes across treatment. Healthy controls were also analysed longitudinally, at baseline and four weeks later, to ensure that there were no changes between time points that might be due to practice effects or other confounders of no interest. As my results indicate, there were no changes in healthy controls longitudinally, which suggests a lack of learning effects.

Patients at follow up relative to baseline showed no increases or decreases in neural activation associated with adaptive or aberrant salience, and no changes in activation associated with the outcome of trials. Across four weeks, healthy controls also showed no increases or decreases in neural activation in any region during adaptive or aberrant salience or during outcome.

3.2.4.6 Region of interest analyses

To specifically assess my proposed hypotheses, a ROI analysis was also executed to explore ventral striatal and dorsolateral PFC activation during aberrant salience processing in patients and healthy controls. No significant clusters were observed following this analysis at either baseline or follow up.

3.2.5 Neural activation underlying salience attribution in responders and non-responders

In these sections, I present data for neural activation underlying salience attribution for patients in relation to response to treatment at four and 12 weeks, to assess the associations of this measure with short- and longer-term treatment response. These analyses will reveal any potential differences in the activation patterns of responders and non-responders at both baseline and follow up, which could aid prediction of treatment response. I also explore the longitudinal changes seen in responders and non-responders, which will reveal whether antipsychotics affect the functional brain activity in these groups differently.

3.2.5.1 Treatment response at four weeks

Treatment response in the following analyses was determined at four weeks and defined according to the Andreasen (2005) criteria.

3.2.5.1.1 Baseline neural activation associated with measures of salience attribution in four-week responders and non-responders

Initially, I conducted random-effects group-level analyses using a one-sample t-test in four-week responders and non-responders separately to investigate group-level activation at baseline associated with each of the contrasts described in Methods (page 108): adaptive salience, aberrant salience, and outcome. This analysis investigates the brain regions activated in association with salience processing in responders and non-responders.

a) Four-week responders

Significant clusters of baseline activation associated with adaptive salience, aberrant salience, and outcome in four-week responders are shown in Table 36 and Figure 16.

Table 36: *Areas of increased neural activation associated with measures of salience and trial outcomes in four-week responders at baseline*

Coordinates are shown in MNI space. P values have been FWE-corrected for multiple comparisons across the whole brain. Values for cluster-level significance are reported.

Brain area	L/R	x	y	z	t	K_E	P value
Adaptive salience (increases)							
Inferior frontal gyrus	L	-38	28	16	7.80	490	0.006
Insula	R	46	8	14	7.02	424	0.011
	R	34	24	12	5.84	308	0.033
Outcome (increases)							
Medial frontal gyrus	L	-4	62	24	7.02	509	0.005

At baseline, four-week responders had increased activation associated with adaptive salience in three significant clusters (Table 36). The first was centred on the left inferior frontal gyrus. The second and third centred on the insula, one of which extended into the right inferior and middle frontal gyri. There were no regions of significantly increased or decreased activation associated with aberrant salience in responders at baseline. At baseline, there was just one region of significantly increased activation associated with the outcome of trials in responders (Table 36). This cluster was centred on the left medial frontal gyrus, extending into the right superior frontal gyrus.

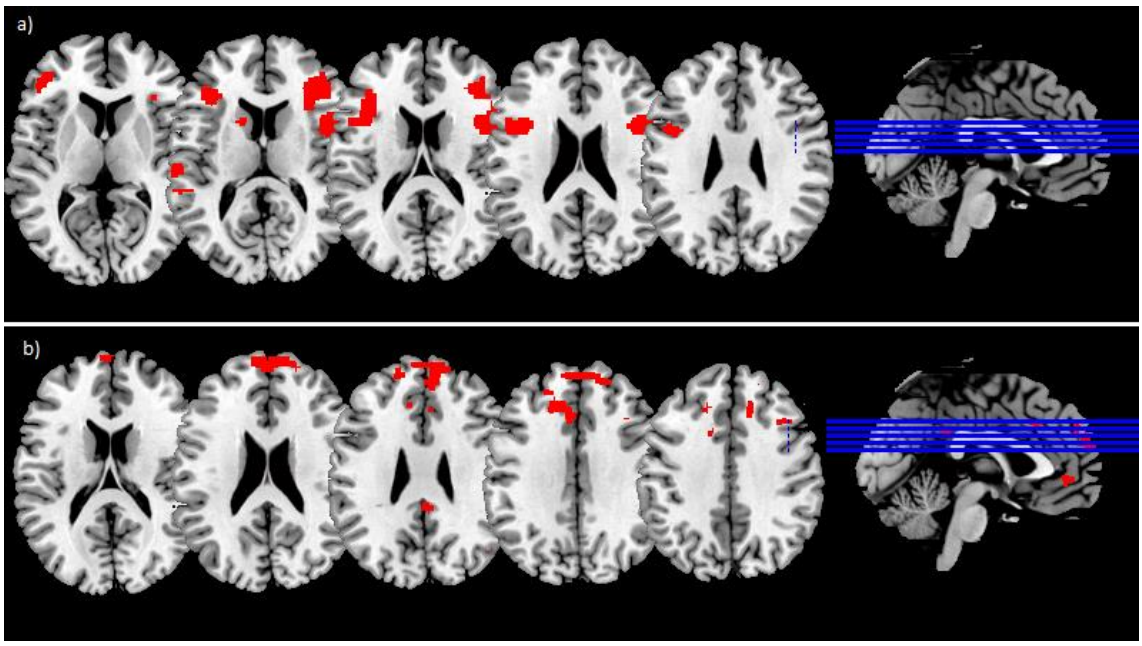

Figure 16: *Areas of activation associated with a) adaptive salience and b) trial outcomes in four-week responders at baseline*

At baseline, a) responders showed increased activation unilaterally in frontal cortex and the insula during adaptive salience processing; b) when presented with the outcome of trials, there was increased activation in the frontal cortex of responders.

b) Four-week non-responders

Significant clusters of baseline activation associated with adaptive salience, aberrant salience, and outcome in four-week non-responders are shown in Table 37 and Figure 17.

Table 37: *Areas of increased baseline neural activation associated with measures of salience in 4-week non-responders*

Coordinates are shown in MNI space. P values have been FWE-corrected for multiple comparisons across the whole brain. Values for cluster-level significance are reported.

Brain area	L/R	x	y	z	t	K_E	P value
Adaptive salience (decreases)							
Cerebellum (declive)	R	14	-70	-28	7.06	367	0.004

At baseline, there was one cluster of decreased activation associated with adaptive salience in four-week non-responders (Table 37). This was centred on the right

cerebellum in the declive, extending into the vermis of the cerebellum. There were no regions of increased activation associated with adaptive salience.

There were no regions of significantly increased or decreased activation associated with aberrant salience or outcome in non-responders at baseline.

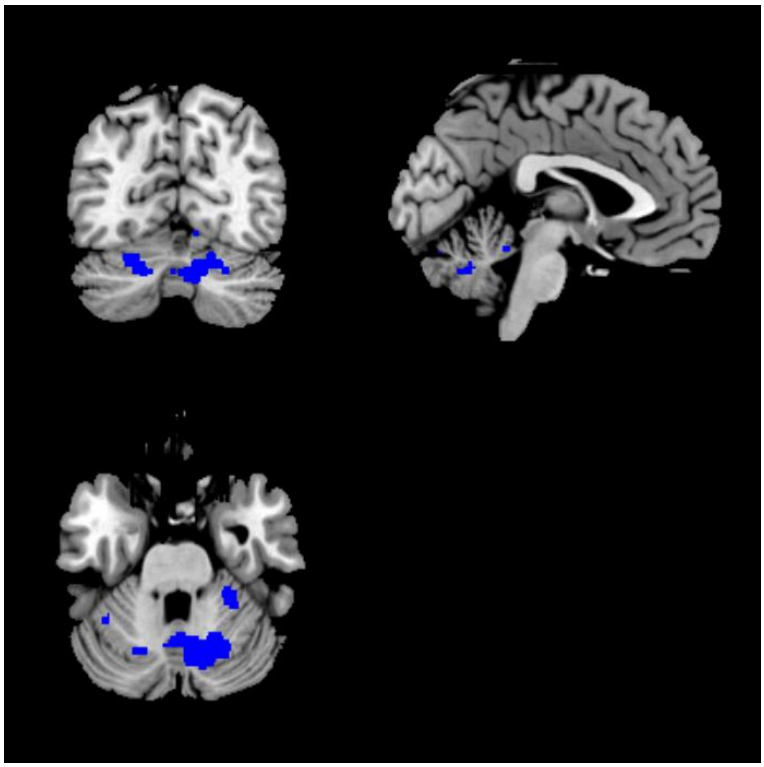

Figure 17: *Areas of decreased neural activation associated with trial outcomes in four-week non-responders at baseline*

At baseline, non-responders showed decreased activation in the declive of the cerebellum during the outcome of trials.

3.2.5.1.2 Cross-sectional comparisons of baseline salience activation in four-week responders and non-responders

I was also interested in potential baseline differences in neural activation associated with response to treatment at four weeks. I explored these differences in two main ways. Firstly, I compared four-week responders with non-responders at baseline. Secondly, I compared each patient group with healthy controls.

To compare the groups, an exploratory voxel-wide search was first performed with p<0.001, uncorrected. Clusters identified were then explored for suprathreshold statistics accepted at p<0.05 (FWE-corrected).

a) Four-week responders versus non-responders

These analyses explored between-group differences in neural activation when comparing four-week responders and non-responders, whilst completing the SAT. Clusters of significantly different activation between responders and non-responders associated with adaptive salience, aberrant salience, and outcome at baseline are shown in Table 38 and Figure 18.

Table 38: *Areas of significantly different neural activation associated with measures of salience and trial outcomes in four-week responders and non-responders at baseline*

Coordinates are shown in MNI space. P values have been FWE-corrected for multiple comparisons across the whole brain. Values for cluster-level significance are reported.

Brain area	L/R	x	y	z	t	K_E	P value
Adaptive salience (responders > non-responders)							
Insula	R	44	4	14	5.75	337	0.042
Cerebellum (declive)	R	4	-60	-22	4.78	360	0.034

At baseline, responders had significantly greater activation than non-responders associated with adaptive salience processing in two clusters (Table 38). The first was centred on the right insula and extended into the right precentral gyrus and superior temporal gyrus. The second cluster was centred on the right declive of the cerebellum, extending into the left declive and right culmen. There were no regions of lower activation in responders than in non-responders during adaptive salience processing at baseline. Furthermore, no significant differences were found between responders and non-responders in activation during aberrant salience or outcome before treatment.

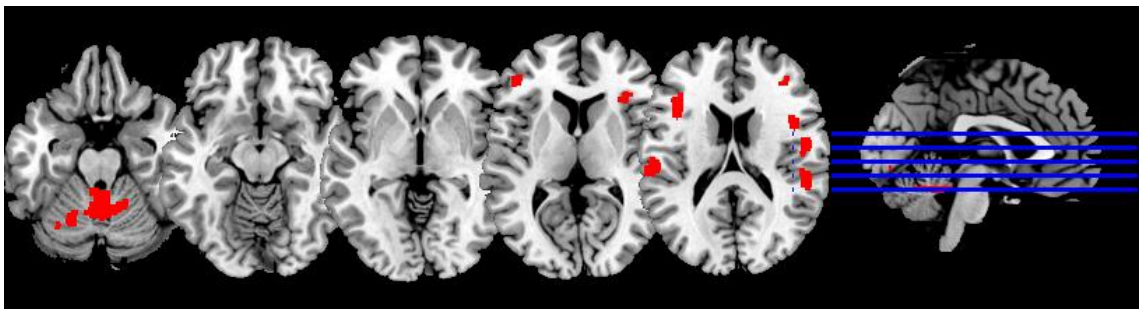

Figure 18: *Regions of significantly different neural activation during adaptive salience in four-week responders compared with non-responders at baseline*

At baseline, responders had greater activation than non-responders in the insula and declive of the cerebellum during adaptive salience processing.

b) Four-week responders versus healthy controls

At baseline, four-week responders compared with healthy controls did not show any differences in activation during adaptive or aberrant salience. There were also no differences in activation elicited by the outcome of trials at baseline.

c) Four-week non-responders versus healthy controls

Clusters of significantly different activation between four-week non-responders and healthy controls associated with adaptive salience, aberrant salience, and outcome at baseline are shown in Table 39 and Figure 19.

Table 39: *Areas of significantly different neural activation associated with measures of salience and trial outcomes in non-responders and healthy controls at baseline*

Coordinates are shown in MNI space. P values have been FWE-corrected for multiple comparisons across the whole brain. Values for cluster-level significance are reported.

Brain area	L/R	x	y	z	t	K_E	P value
Adaptive salience (non-responders < healthy controls)							
Cerebellum (declive)	R	28	-64	-30	6.09	8153	<0.0001

At baseline, there was one region of significantly lower neural activation in four-week non-responders compared with healthy controls during adaptive salience (Table 39). This cluster was centred on the posterior lobe of the right cerebellum (declive) and extended into the left declive. There were no regions of greater neural activation in non-responders compared with healthy controls during adaptive salience at baseline. There were also no significant differences in neural activation between non-responders and healthy controls during aberrant salience or outcome before treatment.

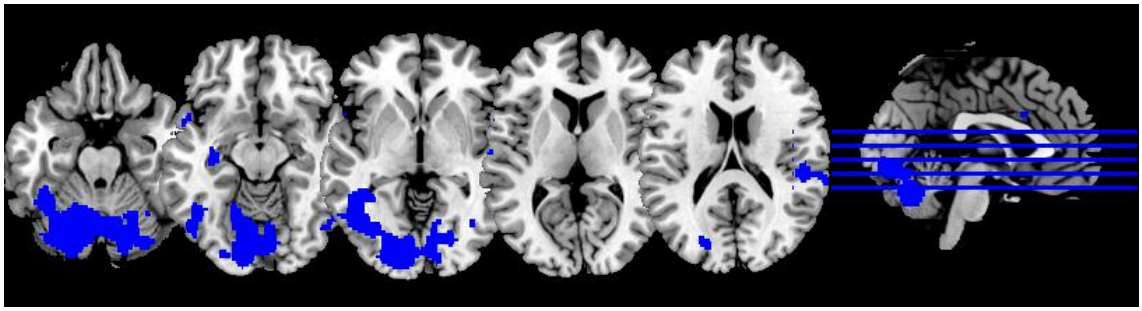

Figure 19: *Regions of significantly different neural activation during adaptive salience in four-week non-responders compared healthy controls at baseline*

At baseline, non-responders had lower activation than healthy controls in the cerebellum during adaptive salience processing.

3.2.5.1.3 Neural activation associated with measures of salience attribution in four-week responders and non-responders at four-week follow up

Initially, random-effects group-level analyses, using a one-sample t test in four-week responders and non-responders separately, were used to investigate group-level activation at follow up associated with each of the contrasts described in Methods (page 108): adaptive salience, aberrant salience, and outcome.

a) Four-week responders

Significant clusters of activation associated with adaptive salience, aberrant salience, and outcome in four-week responders after four weeks of treatment are shown in Table 40 and Figure 20.

Table 40: *Areas of increased neural activation associated with measures of salience and trial outcomes in four-week responders at four-week follow up.*

Coordinates are shown in MNI space. P values have been FWE-corrected for multiple comparisons across the whole brain. Values for cluster-level significance are reported.

Brain area	L/R	x	y	z	t	K_E	P value
Adaptive salience (increases)							
Insula	L	-44	-20	2	6.63	393	0.026
Outcome (increases)							
Middle temporal gyrus	R	52	-16	-12	12.92	1939	<0.0001
	L	-56	-68	2	7.64	1349	<0.0001
	L	-52	2	-22	7.36	776	<0.0001
Inferior parietal lobe	R	48	-38	44	8.67	964	<0.0001
	L	-38	-44	34	5.14	259	0.04
Inferior frontal gyrus	R	48	36	8	8.25	909	<0.0001
	L	-42	42	0	6.18	409	0.007
Posterior cingulate	L	-4	-54	10	7.34	1632	<0.0001
Putamen	R	28	-4	10	6.88	330	0.017

At follow up, in responders there was increased activation associated with adaptive salience in one significant cluster (Table 40). This cluster of significantly increased activation was centred on the left insula, extending into the superior temporal gyrus and the middle occipital gyrus. There were no regions of significantly decreased activation associated with adaptive salience in responders at follow up. There were no regions of significantly increased or decreased activation associated with aberrant salience in responders at follow up.

Several regions were activated in association with the outcome of trials in four-week responders at follow up (Table 40). Nine clusters of significantly increased activation were found in these patients. Both left and right middle temporal gyri were activated, with a single cluster on the right extending into temporal pole and two clusters on the left, one of which extended into the thalamus and the other extending into superior temporal gyrus. The inferior frontal gyrus was also activated in both hemispheres,

extending into middle frontal gyrus on both the left and right. Similarly, there were two clusters of significantly increased activation in the inferior parietal lobe, one in each hemisphere. Another significant cluster of activation was seen in the left posterior cingulate of the limbic lobe, extending into the thalamus. The final cluster was centred on the right putamen, extending into the caudate. There were no regions of significantly decreased activation associated with outcome in responders at follow up.

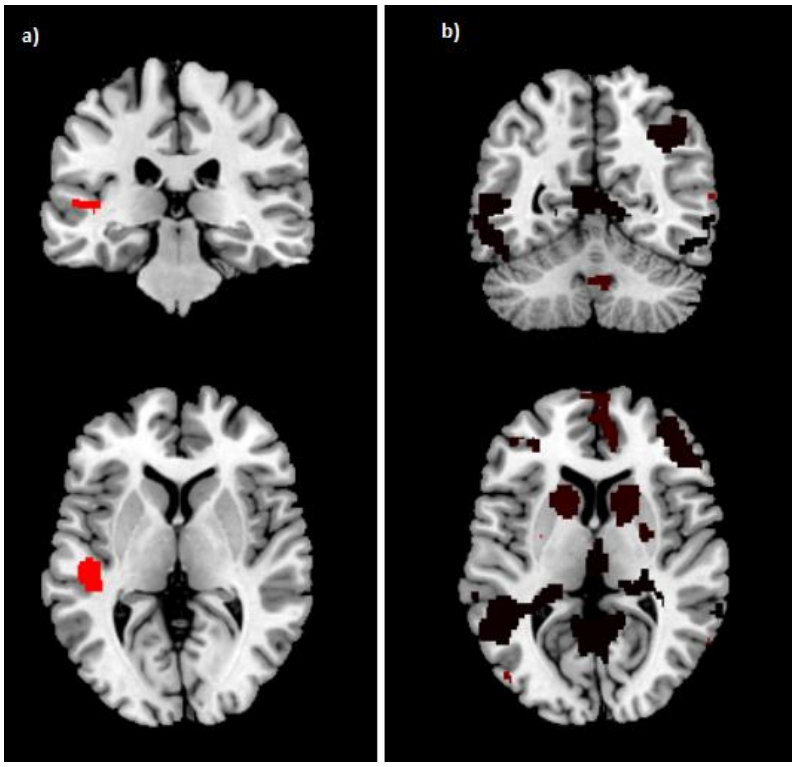

Figure 20: *Areas of activation associated with a) adaptive salience and b) trial outcomes in four-week responders at four-week follow up*

At follow up, responders showed greater activation than non-responders a) during adaptive salience processing in the left temporal cortex and b) in multiple regions in temporal, parietal, and frontal cortex, and in the putamen when presented with the outcome of trials,.

b) Four-week non-responders

Significant clusters of activation associated with adaptive salience, aberrant salience, and outcome in four-week non-responders at follow up are shown in Table 41 and Figure 21.

Table 41: *Areas of increased neural activation associated with measures of salience and trial outcomes in four-week non-responders at 4-week follow up.*

Coordinates are shown in MNI space. P values have been FWE-corrected for multiple comparisons across the whole brain. Values for cluster-level significance are reported.

Brain area	L/R	x	y	z	t	K_E	P value
Aberrant salience (decreased)							
Superior occipital lobe	L	0	-84	12	8.73	236	0.017

After four weeks of treatment, in four-week non-responders there were no regions of increased or decreased activation associated with adaptive salience.

There was one cluster of decreased activation associated with aberrant salience (Table 41). This cluster was centred in the cuneus of the superior occipital lobe, extending into the middle occipital gyrus. There were no regions of significantly increased activation associated with aberrant salience in non-responders after treatment.

There were no regions of significantly increased or decreased activation associated with outcome in non-responders at follow up.

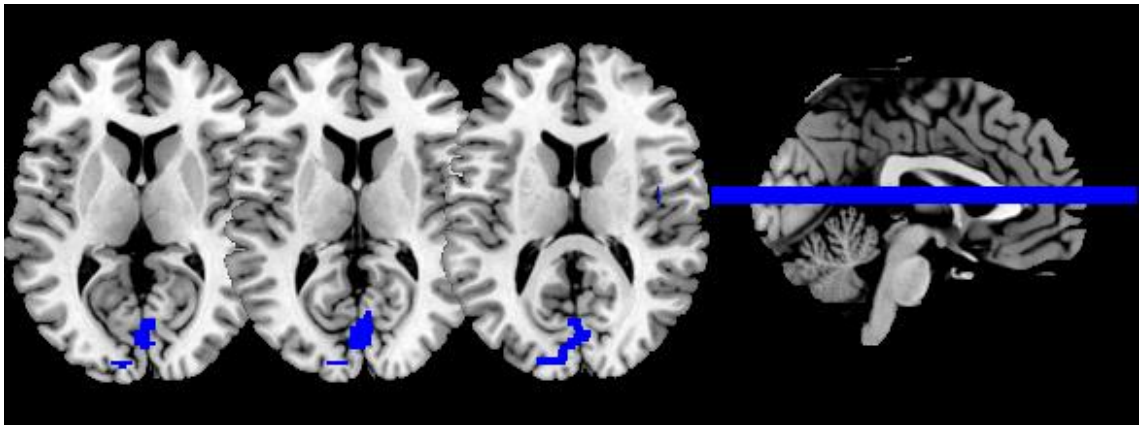

Figure 21: *Areas of increased neural activation associated with aberrant salience in four-week four-week non-responders at four-week follow up*

At follow up, non-responders showed decreased activation in the left occipital lobe.

3.2.5.1.4 Cross-sectional comparisons of four-week follow up salience activation in four-week responders and non-responders

As with baseline data, I also investigated potential differences in neural activation associated with response to treatment at four weeks in two main ways. Firstly, I compared four-week responders with non-responders at follow up. Secondly, I compared each patient group with healthy controls.

To compare the groups, an exploratory voxel-wide search was first performed with $p<0.001$, uncorrected. Clusters identified were then explored for suprathreshold statistics accepted at $p<0.05$ (FWE-corrected).

a) Four-week responders versus non-responders

These analyses explored between-group differences in activation when comparing four-week responders and non-responders, whilst completing the salience attribution task (SAT). Clusters of significantly different activation between responders and non-responders associated with adaptive salience, aberrant salience, and outcome after four weeks of treatment are shown in Table 42 and Figure 22.

Table 42: *Areas of significantly different neural activation associated with measures of salience and trial outcomes in four-week responders and non-responders at four-week follow up.*

Coordinates are shown in MNI space. P values have been FWE-corrected for multiple comparisons across the whole brain. Values for cluster-level significance are reported.

Brain area	L/R	x	y	z	t	K_E	P value
Adaptive salience (responders > non-responders)							
Midbrain	R	6	-2	-12	4.84	739	0.004

After four weeks of treatment, there was one significant cluster of greater activation in four-week responders than in non-responders during adaptive salience processing (Table 42). This cluster was centred on the brain stem, extending across the midbrain,

close to the hypothalamus and substantia nigra. There were no regions of lower activation in responders than in non-responders during adaptive salience processing. Furthermore, no significant differences were found between responders and non-responders in activation during aberrant salience or outcome after treatment.

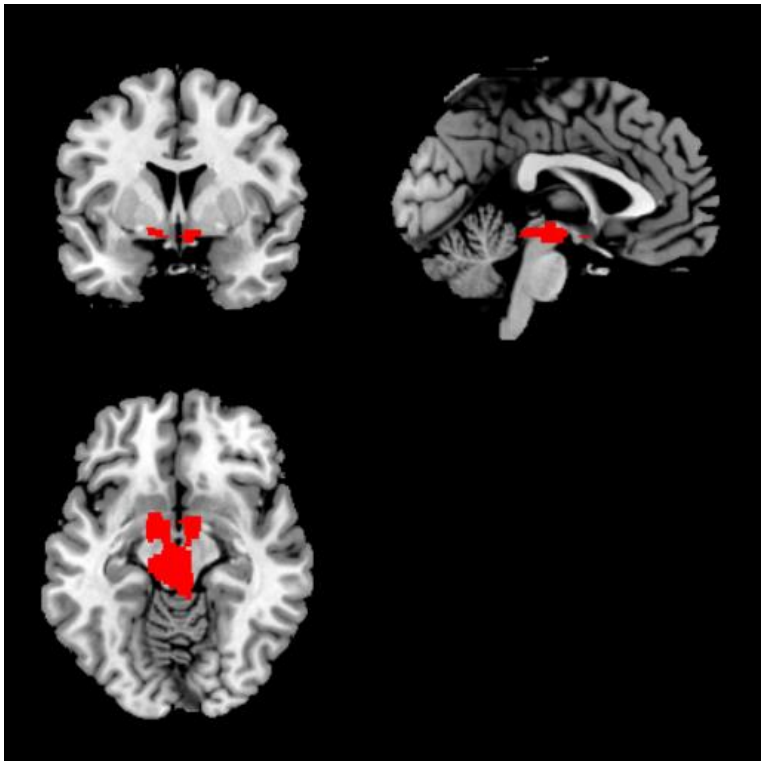

Figure 22: *Regions of significantly different neural activation during adaptive salience in four-week responders compared with non-responders at four-week follow up*

At follow up, responders had greater activation than non-responders in the midbrain during adaptive salience processing.

b) Four-week responders versus healthy controls

Clusters of significantly different activation between four-week responders and healthy controls associated with adaptive salience, aberrant salience, and outcome at four-week follow up are shown in Table 43 and Figure 23.

Table 43: *Areas of significantly different neural activation associated with measures of salience and trial outcomes in four-week responders and healthy controls at four-week follow up.*

Coordinates are shown in MNI space. P values have been FWE-corrected for multiple comparisons across the whole brain. Values for cluster-level significance are reported.

Brain area	L/R	x	y	z	t	K_E	P value
Outcome (responders > healthy controls)							
Middle temporal lobe	L	-44	-42	8	5.80	375	0.027

After four weeks of treatment, neural activation in four-week responders compared with healthy controls did not differ during adaptive or aberrant salience. There was one cluster in which responders had higher activation than healthy controls associated with the outcome of trials (Table 43). This cluster was centred on the middle temporal lobe, extending across the superior temporal gyrus and putamen. There were no regions in which responders had lower activation than healthy controls associated with the outcome of trials.

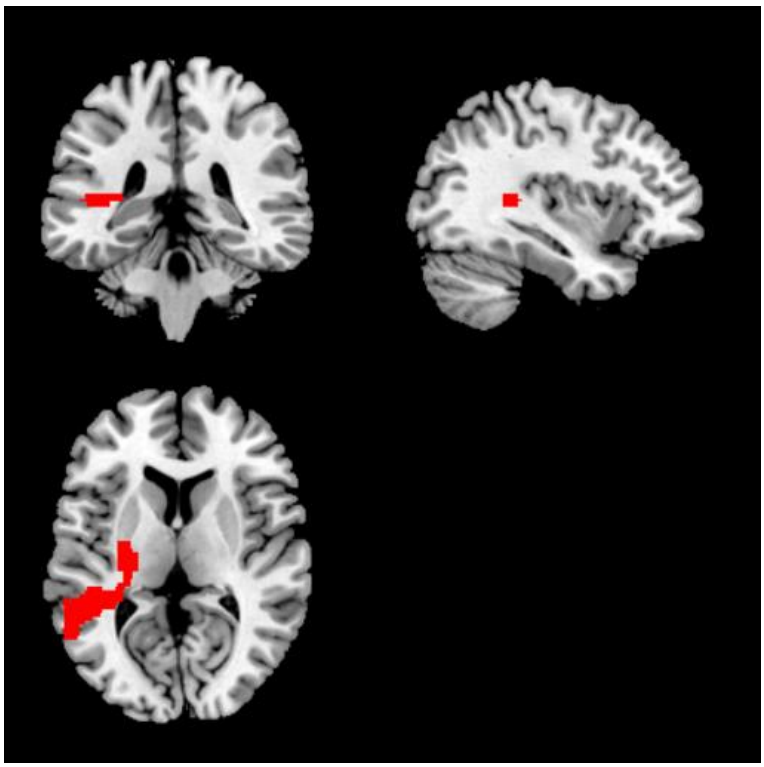

Figure 23: *Areas of significantly different neural activation associated with trial outcomes in 4-week responders and healthy controls at four-week follow up*

At follow up, responders had greater activation than healthy controls in the middle temporal gyrus during presentation of the trial outcomes.

c) Four-week non-responders versus healthy controls

Clusters of significantly different activation between four-week non-responders and healthy controls associated with adaptive salience, aberrant salience, and outcome at four-week follow up are shown in Table 44 and Figure 24.

Table 44: *Areas of significantly different activation associated with measures of salience and trial outcomes in four-week non-responders and healthy controls at four-week follow up.*

Coordinates are shown in MNI space. P values have been FWE-corrected for multiple comparisons across the whole brain. Values for cluster-level significance are reported.

Brain area	L/R	x	y	z	t	K_E	P value
Adaptive salience (non-responders < healthy controls)							
Brainstem	L	-8	-26	-14	4.16	923	<0.0001

After four weeks of treatment, there was one region of significantly lower activation in non-responders compared with healthy controls during adaptive salience (Table 44). This cluster was centred on the brain stem close to the substantia nigra, extending into the right parahippocampal region. There were no regions of greater neural activation in non-responders compared with healthy controls during adaptive salience. There were no significant differences in neural activation between non-responders and healthy controls during aberrant salience or outcome at follow up.

So in responders, normal midbrain dopamine function is maintained following D2 blockade (no difference between responders and controls), whereas in non-responders the midbrain is underactive following treatment, relative to both responders and controls In other words, in non-responders, antipsychotics fail to maintain normal dopamine function. Because this difference wasn't evident at baseline, it must reflect a differential effect of antipsychotic treatment on midbrain dopamine function in responders and non-responders.

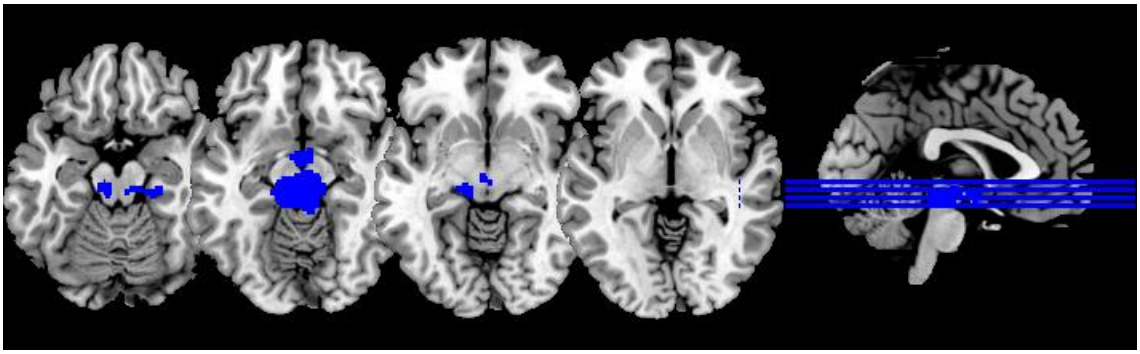

Figure 24: *Areas of significantly different neural activation associated with trial outcomes in 4-week non-responders and healthy controls at four-week follow up*

At follow up, non-responders had lower activation than healthy controls in the midbrain associated with adaptive salience.

3.2.5.1.5 Longitudinal effects of four-week antipsychotic treatment on neural activation underlying salience attribution in four-week responders

Neural activation in responders after four weeks of treatment was compared with baseline scans at which patients were antipsychotic-naïve/minimally treated, to identify any activation changes related to a good response to treatment.

During four weeks of treatment, four-week responders showed no increases or decreases in neural activation associated with adaptive or aberrant salience, and no changes in activation associated with the outcome of trials.

3.2.5.1.6 Longitudinal effects of four-week antipsychotic treatment on neural activation underlying salience attribution in four-week non-responders

Neural activation in four-week non-responders after four weeks of treatment was compared with baseline scans at which patients were antipsychotic-naïve/minimally treated, to identify any activation changes related with a poor response to treatment.

Clusters of significantly changed activation in responders associated with adaptive salience, aberrant salience, and outcome are shown in Table 45 and Figure 25.

Table 45: *Areas of significantly altered neural activation following treatment associated with measures of salience and trial outcomes in four-week responders and non-responders*

Coordinates are shown in MNI space. P values have been FWE-corrected for multiple comparisons across the whole brain. Values for cluster-level significance are reported.

Brain area	L/R	x	y	z	t	K_E	P value
a) Responders							
No suprathreshold clusters							
b) Non-responders							
Adaptive salience (baseline < follow up)							
Cerebellum (declive)	L	-20	-70	-34	19.68	958	<0.0001
	R	26	-34	-30	8.77	362	0.001

During four weeks of treatment, four-week non-responders had increased neural activation at follow up compared with baseline in two clusters during adaptive salience processing (Table 45). These clusters were both in the cerebellum, with one in each hemisphere. There were no regions of decreased activation at follow up associated with adaptive salience. There were also no regions of either increased or decreased activation following treatment associated with aberrant salience or the outcomes of trials.

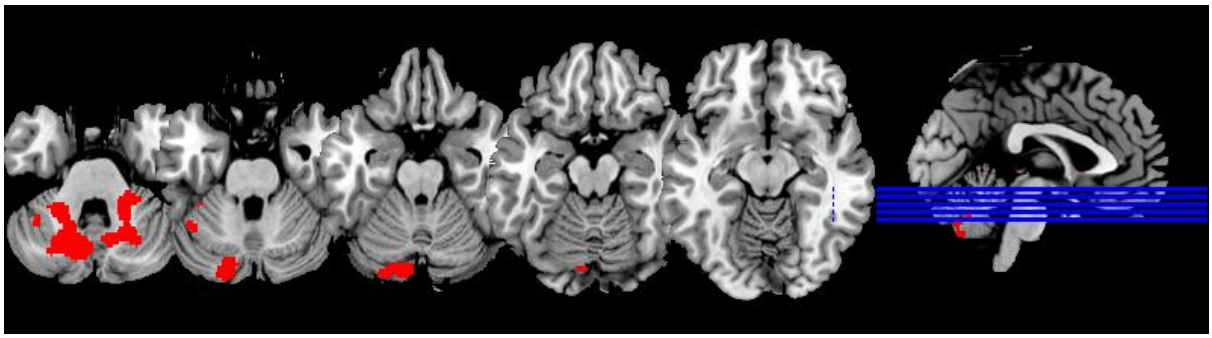

Figure 25: *Areas of significantly altered neural activation following treatment associated with adaptive salience in four-week non-responders*

Non-responders showed decreases in bilateral cerebellum during adaptive salience processing following four weeks of antipsychotic treatment.

3.2.5.1.7 Region of interest analyses

To specifically assess my proposed hypotheses, a ROI analysis was also executed to explore ventral striatal and dorsolateral PFC activation during aberrant salience processing in four-week responders and non-responders. No significant clusters were observed following this analysis at baseline or four-week follow up.

3.2.5.2 Treatment response at 12 weeks

Treatment response in the following analyses was determined at 12 weeks, using the PPHS assessment.

3.2.5.1.1 Baseline neural activation associated with measures of salience attribution in 12-week responders and non-responders

Initially, random-effects group-level analyses, using a one-sample t test in 12-week responders and non-responders separately, were used to investigate group-level activation at baseline associated with each of the contrasts described in Methods (page 108): adaptive salience, aberrant salience, and outcome.

a) Twelve-week responders

At baseline, there was no significant activation in 12-week responders during adaptive salience, aberrant salience or outcome.

b) Twelve-week non-responders

At baseline, there was no significant activation in 12-week non-responders during adaptive salience, aberrant salience or outcome.

3.2.5.1.2 Cross-sectional comparisons of baseline salience activation in 12-week responders and non-responders

I was also interested in potential differences in neural activation associated with response to treatment at 12 weeks. I explored these differences in two main ways. Firstly, I compared 12-week responders with non-responders at baseline. Secondly, I compared each patient group with healthy controls.

To compare the groups, an exploratory voxel-wide search was first performed with $p<0.001$, uncorrected. Clusters identified were then explored for suprathreshold statistics accepted at $p<0.05$ (FWE-corrected).

a) Twelve-week responders versus non-responders

These analyses explored between-group differences in neural activation when comparing 12-week responders and non-responders, whilst completing the salience

attribution task (SAT). Clusters of significantly different activation between responders and non-responders associated with adaptive salience, aberrant salience, and outcome at baseline are shown in Table 46 and Figure 26.

Table 46: *Areas of significantly different neural activation associated with measures of salience and trial outcomes in 12-week responders and non-responders at baseline*

Coordinates are shown in MNI space. P values have been FWE-corrected for multiple comparisons across the whole brain. Values for cluster-level significance are reported.

Brain area	L/R	x	y	z	t	K_E	P value
Adaptive salience (responders > non-responders)							
Superior temporal lobe	L	-56	-34	20	6.67	539	0.004
Middle occipital lobe	L	-20	-78	18	5.87	293	0.042

At baseline, responders had significantly greater activation than non-responders associated with adaptive salience processing in two clusters (Table 46). The first was centred on the left superior temporal lobe in the region of the insula, extending into the left supramarginal gyrus and left postcentral gyrus. The second cluster was centred on the left middle occipital lobe extending into the cuneus. There were no regions of lower activation in responders than in non-responders during adaptive salience processing at baseline. Furthermore, no significant differences were found between responders and non-responders in activation during aberrant salience or outcome before treatment.

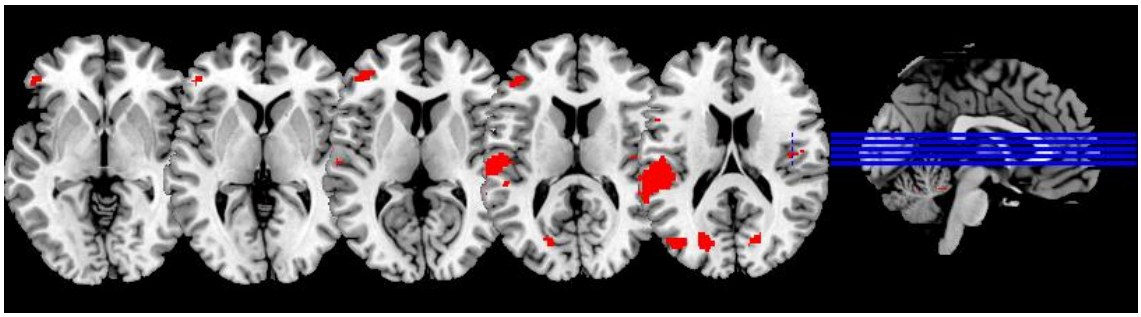

Figure 26: *Areas of significantly different neural activation associated with adaptive salience in 12-week responders and non-responders at baseline*

At baseline, responders had greater activation than non-responders in the superior temporal lobe and middle occipital lobe during adaptive salience processing.

b) Twelve-week responders versus healthy controls

At baseline, 12-week responders compared with healthy controls did not show any differences in activation during adaptive or aberrant salience. There were also no differences in activation elicited by the outcome of trials at baseline.

c) Twelve-week non-responders versus healthy controls

Clusters of significantly different activation between 12-week non-responders and healthy controls associated with adaptive salience, aberrant salience, and outcome at baseline are shown in Table 47 and Figure 27.

Table 47: *Areas of significantly different neural activation associated with measures of salience and trial outcomes in 12-week non-responders and healthy controls at baseline*

Coordinates are shown in MNI space. P values have been FWE-corrected for multiple comparisons across the whole brain. Values for cluster-level significance are reported.

Brain area	L/R	x	y	z	t	K_E	P value
Adaptive salience (non-responders < healthy controls)							
Cerebellum (declive)	L	-16	-76	-26	5.48	3810	<0.0001

At baseline, there was one region of significantly lower neural activation in 12-week non-responders compared with healthy controls during adaptive salience (Table 47). This cluster was centred on the declive of the left cerebellum and extended into the left lingual gyrus. There were no regions of greater neural activation in non-responders compared with healthy controls during adaptive salience at baseline. There were also no significant differences in neural activation between non-responders and healthy controls during aberrant salience or outcome before treatment.

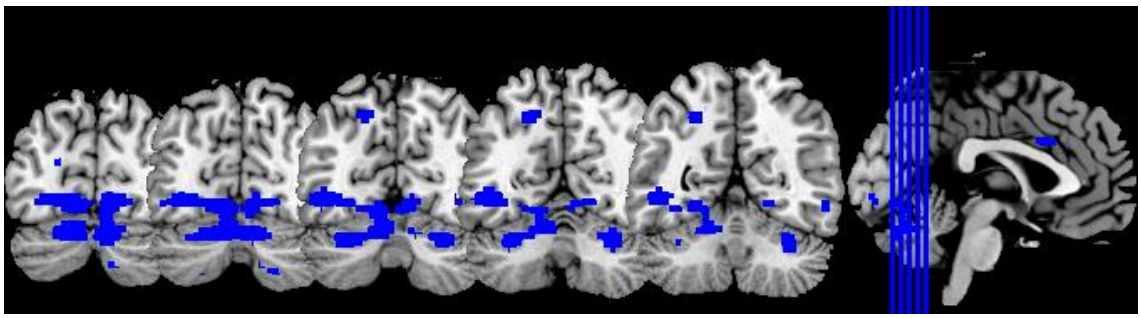

Figure 27: *Areas of significantly different neural activation associated with adaptive salience in 12-week non-responders and healthy controls at baseline*

At baseline, non-responders had lower activation than healthy controls in the cerebellum during adaptive salience processing.

3.2.5.1.3 Neural activation associated with measures of salience attribution in 12-week responders and non-responders at four-week follow up

Initially, random-effects group-level analyses, using a one-sample t-test in 12-week responders and non-responders separately, were used to investigate group-level activation at four-week follow up associated with each of the contrasts described in Methods (page 108): adaptive salience, aberrant salience, and outcome.

a) Twelve-week responders

Significant clusters of activation associated with adaptive salience, aberrant salience, and outcome in 12-week responders after four weeks of treatment are shown in Table 48 and Figures 28a/b.

Table 48: *Areas of increased neural activation associated with measures of salience and trial outcomes in 12-week responders at 4-week follow up.*

Coordinates are shown in MNI space. P values have been FWE-corrected for multiple comparisons across the whole brain. Values for cluster-level significance are reported.

Brain area	L/R	x	y	z	t	K_E	P value
Adaptive salience (increases)							
Superior temporal lobe	L	-42	-26	2	10.84	507	<0.0001
Adaptive salience (decreases)							
Superior frontal gyrus	L	-14	42	36	7.75	214	0.017
Outcome (increases)							
Cerebellum	R	2	-82	-28	11.60	423	<0.0001
Middle temporal gyrus	R	62	-50	-4	12.20	207	0.02
	R	64	-18	-12	15.47	157	0.057**
Inferior parietal lobe	R	50	-40	38	8.84	162	0.051**
Inferior frontal gyrus	R	48	42	4	12.22	160	0.053**

At follow up, in responders there was increased activation associated with adaptive salience in one significant cluster (Table 48). This cluster of significantly increased activation was centred on the left superior temporal lobe. There were also one significant cluster of significantly decreased activation associated with adaptive salience in responders at follow up. This cluster was centred on the left superior frontal gyrus. There were no regions of significantly increased or decreased activation associated with aberrant salience in responders at follow up.

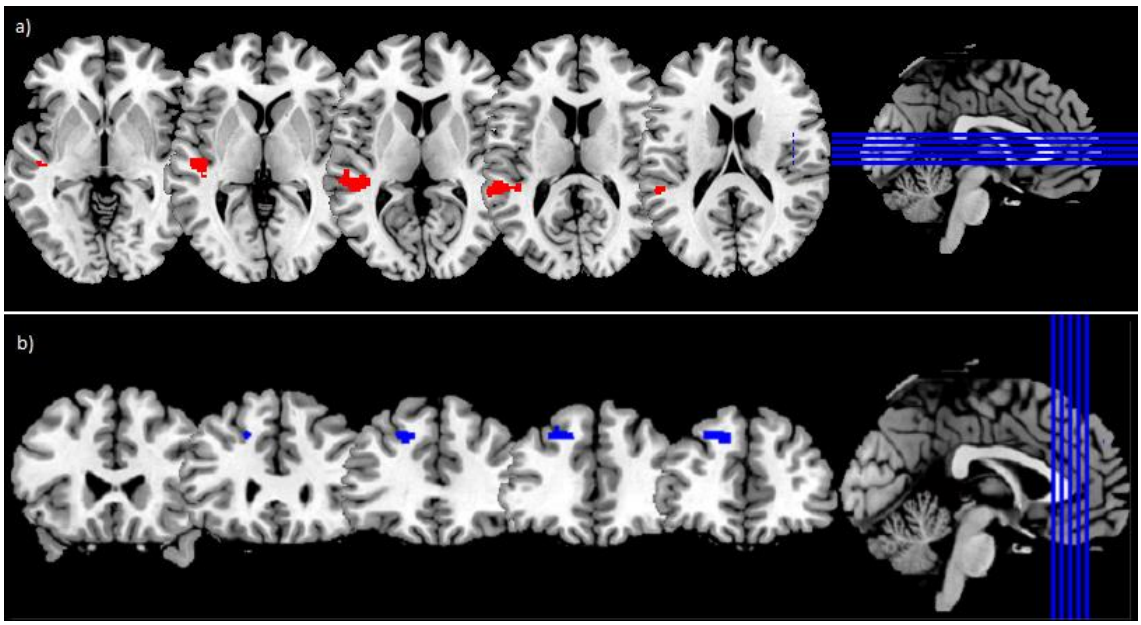

Figure 28a: *Areas of significantly increased (red) and decreased (blue) neural activation associated with adaptive salience in 12-week responders at four-week follow up*

At follow up, adaptive salience processing in responders was associated with a) increased activation in superior temporal lobe and b) decreased activation in the superior frontal gyrus.

There were two regions of significantly increased activation in association with the outcome of trials in responders at follow up, as well as three clusters of activation that neared significance (Table 48). The first significant cluster was centred on the cerebellum. The second was centred on the right middle temporal gyrus. There was also another cluster of activation that neared significance in the right middle temporal gyrus. A cluster of activation in the right supramarginal gyrus of the inferior parietal gyrus neared significance, as did a cluster of activation in the right inferior frontal gyrus, which extended into the middle frontal gyrus. There were no regions of significantly decreased activation associated with outcome in responders at follow up.

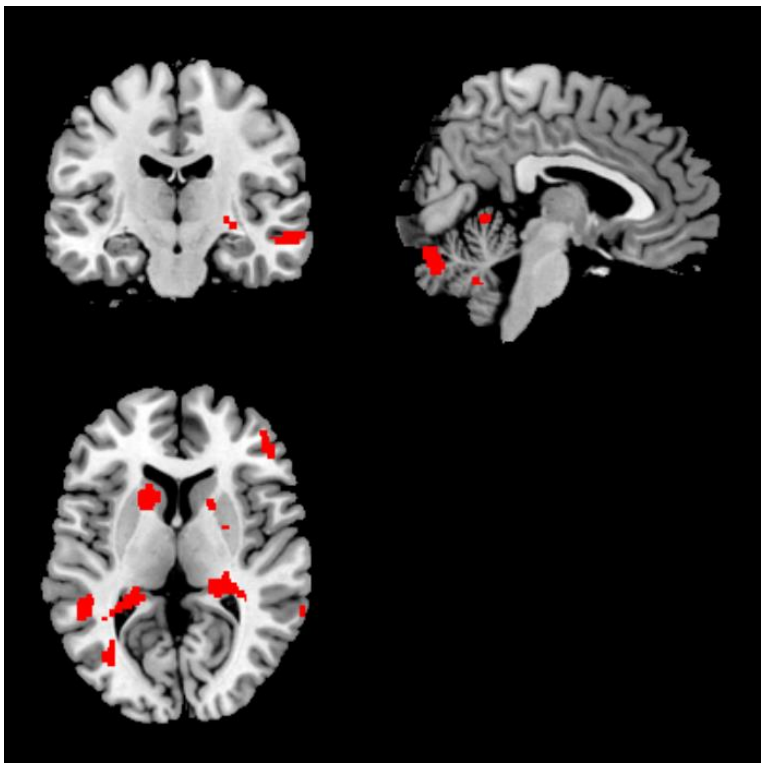

Figure 28b: *Areas of significantly increased neural activation associated with the outcome of trials in 12-week responders at four-week follow up*

At follow up, the outcome of trials in responders was associated with increased activation in the cerebellum, middle temporal gyrus, inferior parietal lobe, and inferior frontal gyrus.

b) Twelve-week non-responders

At follow up, there was no significant activation in 12-week non-responders during adaptive salience, aberrant salience or outcome.

3.2.5.1.4 Cross-sectional comparisons of salience activation in 12-week responders and non-responders at four-week follow up

As with baseline data, I also investigated potential differences in neural activation associated with response to treatment at 12 weeks in two main ways. Firstly, I compared 12-week responders with non-responders at four-week follow up. Secondly, I compared each patient group with healthy controls.

To compare the groups, an exploratory voxel-wide search was first performed with p<0.001, uncorrected. Clusters identified were then explored for suprathreshold statistics accepted at p<0.05 (FWE-corrected).

a) Twelve-week responders versus non-responders

After four weeks of treatment, 12-week responders compared with non-responders did not show any differences in activation during adaptive or aberrant salience. There were also no differences in activation elicited by the outcome of trials at follow up.

b) Twelve-week responders versus healthy controls

After four weeks of treatment, 12-week responders compared with healthy controls did not show any differences in activation during adaptive or aberrant salience. There were also no differences in activation elicited by the outcome of trials at follow up.

c) Twelve-week non-responders versus healthy controls

Clusters of significantly different activation between 12-week non-responders and healthy controls associated with adaptive salience, aberrant salience, and outcome at four-week follow up are shown in Table 49 and Figure 29.

Table 49: *Areas of significantly different neural activation associated with measures of salience and trial outcomes in 12-week non-responders and healthy controls at 4-week follow up.*

Coordinates are shown in MNI space. P values have been FWE-corrected for multiple comparisons across the whole brain. Values for cluster-level significance are reported.

Brain area	L/R	x	y	z	t	K_E	P value
Aberrant salience (non-responders < healthy controls)							
Frontal lobe	L	-18	-38	30	5.44	903	0.001
Posterior cingulate/thalamus	R	18	-60	12	4.65	606	0.008

After four weeks of treatment, there were no regions of significantly different neural activation between 12-week non-responders and healthy controls during adaptive salience processing. There were two clusters of significantly lower neural activation in 12-week non-responders compared with healthy controls during aberrant salience (Table 49). The first cluster was centred on left frontal lobe, extending into the inferior parietal lobule and right precuneus. The second cluster was centred on right posterior cingulate, extending into bilateral thalamus. There were no regions of greater neural activation in non-responders compared with healthy controls during aberrant salience. There were no significant differences in neural activation between non-responders and healthy controls during outcome at follow up.

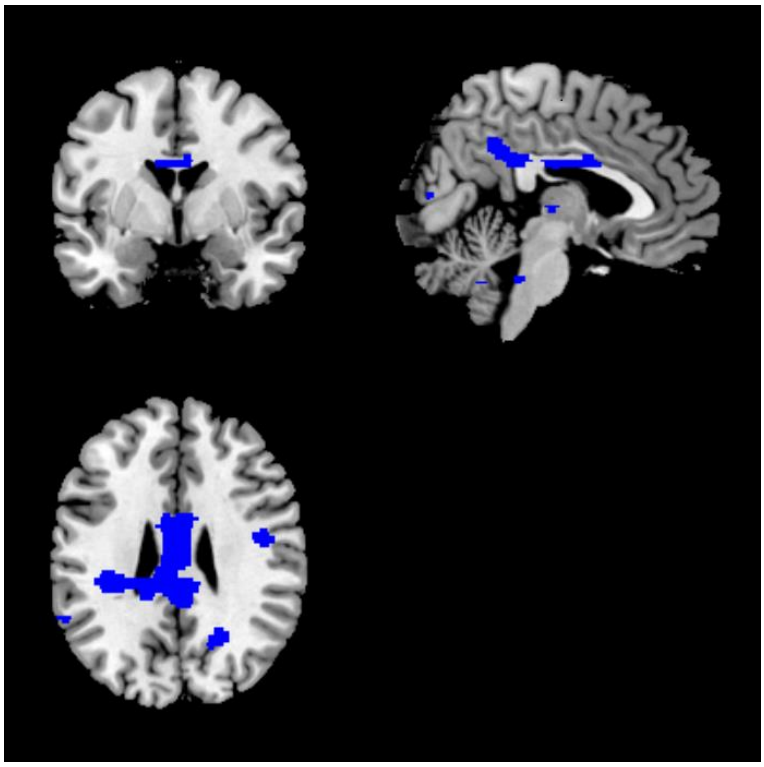

Figure 29: *Areas of significantly different neural activation in 12-week non-responders compared with healthy controls associated with aberrant salience at four-week follow up*

At follow up, the outcome of trials in responders was associated with increased activation in the cerebellum, middle temporal gyrus, inferior parietal lobe, and inferior frontal gyrus.

3.2.5.1.5 Longitudinal effects of four-week antipsychotic treatment on neural activation underlying salience attribution in 12-week responders

In 12-week responders, I compared neural activation after four weeks of treatment in with baseline scans at which patients were antipsychotic-naïve/minimally treated. This aimed to identify activation changes related to a good response to treatment. Clusters of significantly changed activation in 12-week responders associated with adaptive salience, aberrant salience, and outcome are shown in Table 50 and Figure 30.

Table 50: *Areas of significantly altered neural activation following treatment associated with measures of salience and trial outcomes in 12-week responders and non-responders*

Coordinates are shown in MNI space. P values have been corrected for multiple comparisons across the whole brain. Values for cluster-level significance are reported.

Brain area	L/R	x	y	z	t	K_E	P value
a) Responders							
No suprathreshold clusters							
b) Non-responders							
Outcome (baseline > follow up)							
Middle occipital gyrus	L	-40	-78	0	3.87	186	0.033

During four weeks of treatment, 12-week responders showed no increases or decreases in neural activation associated with adaptive or aberrant salience, and no changes in activation associated with the outcome of trials.

3.2.3.1.6 Longitudinal effects of four-week antipsychotic treatment on neural activation underlying salience attribution in 12-week non-responders

After four weeks of treatment, 12-week non-responders had decreased neural activation in one cluster during outcome (Table 50). This cluster was centred in the left middle occipital gyrus. There were no regions of increased neural activation associated

with treatment in non-responders during the outcome of trials. There were also no regions of altered activation associated with either adaptive or aberrant salience.

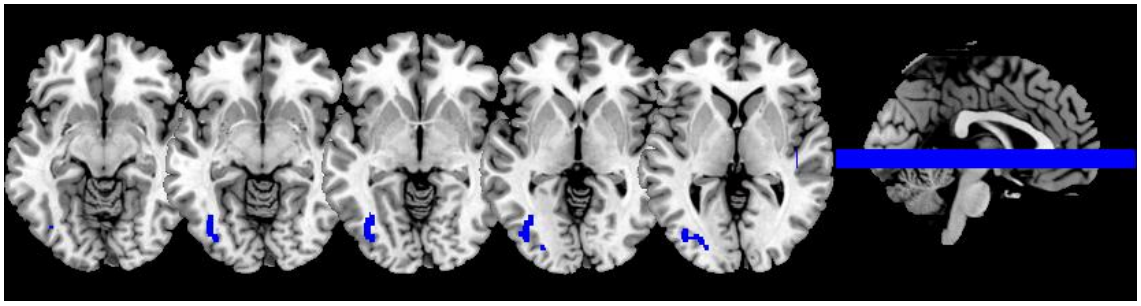

Figure 30: *Areas of significantly altered neural activation following treatment associated with outcome to trials in 12-week non-responders*

Non-responders showed decreases in the middle occipital gyrus following four weeks of antipsychotic treatment.

3.2.6 Chapter summary

In this chapter, I have described the effects of antipsychotic treatment on behavioural measures of salience attribution and the associated neural activation. Furthermore, I explored the relationships between these measures at baseline and after four weeks of treatment, and treatment response assessed at four or 12 weeks.

At the behavioural level, there were relatively few differences in salience attribution measures between the whole patient group and healthy controls at either baseline or follow up. Patients had similar levels of implicit adaptive salience but had lower levels of explicit adaptive salience at baseline and follow up, suggesting they were less conscious of the relationships between cues and reward that their responses indicated they had learned, even after treatment. Unexpectedly, there was no evidence of increased aberrant salience in the patient group at either baseline or follow up. Furthermore, in the patient group overall, treatment was not associated with significant longitudinal changes in any of the salience measures.

More striking results were evident when patients were subdivided according to their response to treatment. A good response at both four weeks and 12 weeks was associated with higher implicit adaptive salience scores at baseline. Responders at four weeks showed a significant decrease in implicit aberrant salience with treatment, which was not seen in non-responders. After four weeks of treatment, responders had significantly lower levels of implicit aberrant salience than non-responders. Responders at 12 weeks also showed a significant reduction in implicit aberrant salience that was not seen in 12-week non-responders.

In both the total patient group and in healthy controls, trial outcome was associated with activation in frontal regions, although the precise location of the regions differed between the groups. In healthy controls, adaptive salience was associated with activation in the superior temporal gyrus. In patients neither adaptive nor aberrant salience were associated with significant activation. Comparison of the patient and control groups failed to reveal any significant differences in activation associated with any salience measure, either at baseline or follow up.

As with the behavioural data, differences became much more apparent when the patients were subdivided according to therapeutic response at four weeks. When compared at baseline, responders showed greater activation than non-responders when processing adaptive salience in the insula and cerebellum. At follow up, responders had higher activation in association with adaptive salience in the midbrain. There were no longitudinal changes in activation with treatment in responders, whereas non-responders showed bilateral increases in cerebellar activation. There were no significant differences between responders and healthy controls at baseline, but at follow up, responders showed greater activation during the presentation of trial outcomes in the middle temporal lobe. Non-responders showed lower activation during adaptive salience than healthy controls in the cerebellum at baseline, and in the brainstem at four-week follow up.

When patients were subdivided by their response at 12 weeks, responders and non-responders differed in activation during adaptive salience processing in the superior temporal and middle occipital lobes at baseline, but there were no differences at follow up. Similar to four-week responders, those designated as responders at 12 weeks did not show any differences compared with healthy controls at either baseline or follow up. Non-responders, however, had lower activation during adaptive salience compared with healthy controls at baseline and follow up. At baseline, this was found in the cerebellum, but at follow up there was lower activation in the frontal lobe and posterior cingulate.

The results in this chapter suggest that while there are some differences between patients and controls in salience processing, there are more striking behavioural and neural differences when patients are subdivided according to their response to antipsychotic treatment. Moreover, at both the behavioural and neural level, these differences are more evident in relation to adaptive than aberrant salience processing.

3.3 The effects of antipsychotics on resting cerebral blood flow (rCBF) using continuous spin labelling (cASL)

In this chapter, I present the results from the analysis of the perfusion data, using a resting-state ASL technique that allows the visualisation CBF in patients and healthy controls at rest.

I begin by presenting cross-sectional data comparing antipsychotic-naïve patients with healthy controls. This will explore whether rCBF in patients before treatment differs from rCBF in healthy individuals (suggesting potential perfusion abnormalities relating to the pathophysiology of their illness). I then present a cross-sectional analysis of patients after four weeks of treatment compared with healthy controls. This comparison will explore whether any differences between these groups, that may have been present at baseline, are still present following four weeks treatment.

In this chapter, I will then present longitudinal analyses exploring the effect of antipsychotic medication on rCBF in patients. In these analyses, I compare rCBF maps at baseline and follow up in the same patients. For completion, and to check stability of rCBF measurements over the duration for which patients were treated, I also present longitudinal assessments of healthy individuals, comparing baseline and follow up scans for any altered patterns of rCBF over four weeks.

Finally, I will assess the relationship between antipsychotic treatment response and rCBF. I do this by first exploring patterns of rCBF in good and poor treatment responders cross-sectionally at baseline and follow up, with one another and with healthy controls. I then assess longitudinal changes in rCBF seen in each of these groups individually. These analyses are carried out with response to treatment assessed at four weeks and at 12 weeks, to investigate short- and longer-term outcomes.

For each of these analyses, I first explore the whole brain in a voxel-wise manner. I then present region of interest (ROI) analyses for the hippocampus, caudate, and putamen.

Hypotheses tested:

- At baseline, I would expect to see decreased striatal perfusion and increased frontal and hippocampal perfusion in patients compared with healthy controls.
- At follow up, I would expect increased resting striatal perfusion and decreased frontal and hippocampal perfusion in patients compared with healthy controls.

To assess the relationship between perfusion and clinical or behavioural measures, I conducted correlational analyses using extracted values for the whole brain and for the clusters where significant increases or decreases were observed. Where variables were normally distributed, Pearson's correlations were calculated. Where variables were non-normally distributed, Spearman's correlations were calculated.

As previously mentioned, one participant did not take part in the cASL arm of the study (Table 51). Unless otherwise stated, all participants who completed the cASL paradigm (n=24) were included in the analyses.

Table 51: *Patients not included in cASL analysis*

Patient ID	Reason for non-inclusion
2208	Error in writing image files – images not available for analysis

3.3.1 Resting CBF in patients and healthy controls

I first considered patterns of resting perfusion in the entire patient group and the healthy controls. These analyses try to identify the presence of any abnormalities in patterns of rCBF in patients with FEP before treatment. They also investigate the effects of antipsychotic treatment on rCBF in a group of previously untreated patients with FEP.

3.3.1.1 Global rCBF in patients and healthy controls at baseline

At baseline, patients had a mean global rCBF of 314.42 ml blood/100g tissue/minute (S.D. 74.74), whilst healthy controls had a mean of 312.84 ml blood/100g tissue/minute (S.D. 77.80). These values were not significantly different ($t(44)=0.031$, $p=0.98$).

3.3.1.2 Cross-sectional comparisons of rCBF in patients and healthy controls at baseline

Initially, patients and healthy controls were compared at baseline using an exploratory voxel-wide search with $p<0.01$, uncorrected. Clusters identified were then explored for suprathreshold statistics and accepted at $p<0.05$. These were FWE-corrected for multiple comparisons, covarying for global rCBF.

Figure 31 and table 52 show clusters of significantly different rCBF in patients and healthy controls at baseline.

Table 52: *Areas of significantly different rCBF in patients and healthy controls at baseline*

Coordinates are shown in MNI space. P values have been FWE-corrected for multiple comparisons across the whole brain. Values for cluster-level significance are reported.

Brain area	L/R	x	y	z	t	K_E	P value
Patients < Healthy controls							
Middle temporal gyrus	L	-46	-68	28	6.28	4753	<0.0001
Precuneus	L	-6	-54	38	4.07	1662	0.02

Patients showed no regions of greater rCBF than healthy controls. However, they did show two clusters of lower rCBF than healthy controls. The first cluster was centred on the left middle temporal gyrus, extending into the superior temporal lobe and the left inferior parietal lobe. The second cluster was centred on the left precuneus of the parietal lobe, extending into the left frontal lobe.

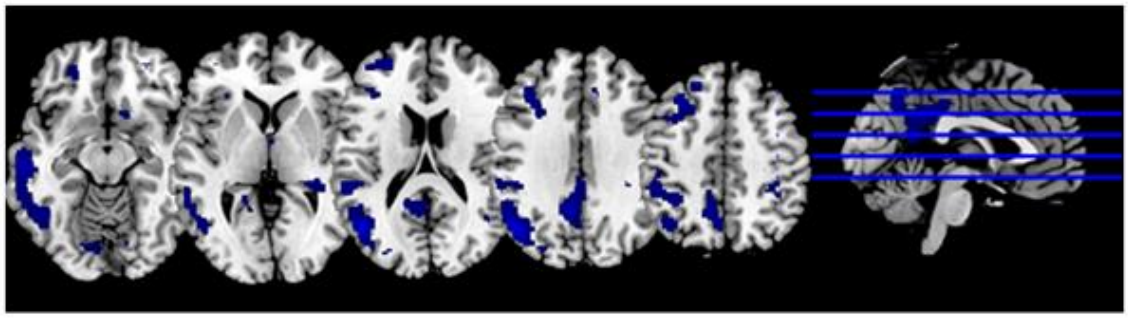

Figure 31: *Perfusion differences between patients and healthy controls at baseline*

Lower resting perfusion (blue) in patients compared with healthy controls before treatment was seen in temporal and parietal regions

3.3.1.3 Global rCBF in patients and healthy controls at follow up

Patients and healthy control did not have significantly different global rCBF at follow up ($t(39)=-0.98$, $p=0.33$). Patients had a mean of 296.64 ml blood/100g tissue/minute (S.D. 60.21) and healthy controls had a mean of 316.65 ml blood/100g tissue/minute (S.D. 72.22).

3.3.1.4 Cross-sectional comparisons of rCBF in patients and healthy controls at follow up

As at baseline, patients and healthy controls were compared at follow up using an exploratory voxel-wide search with p<0.01, uncorrected. Clusters identified were then explored for suprathreshold statistics and accepted at p<0.05. These were FWE-corrected for multiple comparisons, covarying for global rCBF.

Table 53: *Areas of significant rCBF differences in patients and healthy controls at follow up*

Coordinates are shown in MNI space. P values have been FWE-corrected for multiple comparisons across the whole brain. Values for cluster-level significance are reported.

Brain area	L/R	x	y	z	t	K_E	P value
Patients > Healthy controls							
Superior temporal lobe	L	-44	-6	-12	3.98	2490	0.003

Figure 32 and Table 53 show clusters of significantly different rCBF in patients and healthy controls at follow up.

Patients showed significantly greater rCBF than healthy controls in one cluster. This cluster was centred on the left superior temporal lobe and extended into the left temporal pole. There were no regions of significantly lower rCBF in patients compared with healthy controls at follow up.

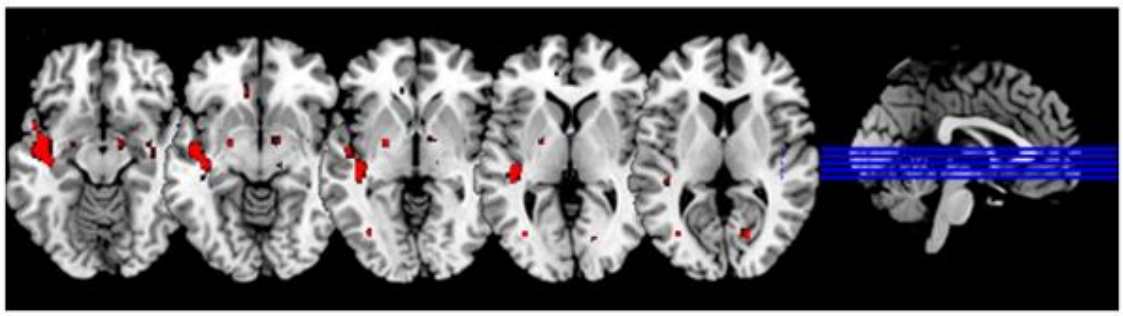

Figure 32: *Perfusion differences between patients and healthy controls at follow up*

Higher resting perfusion (red) in patients compared with healthy controls after treatment was seen in temporal lobe.

3.3.1.5 Correlations between rCBF and clinical measures in patients

Significant clusters from the above cross-sectional analyses were extracted and correlational analyses with clinical and behavioural measures were conducted to explore relationships between differences in these regions and clinical changes in patients.

(i) PANSS scores

There were no significant correlations between PANSS scores and clusters in which there was either baseline or follow up rCBF differences between patients and healthy controls.

(ii) CGI

There were no significant correlations between CGI scores and clusters in which there was either baseline or follow up rCBF differences between patients and healthy controls.

(iii) PSP

There were no significant correlations between PSP scores and clusters in which there was either baseline or follow up rCBF differences between patients and healthy controls.

(iv) CDSS

Lower perfusion at baseline in the middle temporal gyrus was significantly correlated with higher scores on the CDSS at baseline ($r=-0.51$, $p=0.018$), indicating that the presence of depressive symptoms was associated with lower perfusion in this region. There were no significant correlations between any other clusters in which rCBF was significantly different in patients compared with healthy controls and CDSS scores at either baseline or follow up.

(v) Antipsychotic dose

Higher perfusion in the superior temporal lobe at follow up was significantly associated with higher antipsychotic dose ($n=14$, $r=0.56$, $p=0.038$).

(vi) Salience attribution

There were no significant correlations between clusters in which rCBF was significantly different in patients compared with healthy controls and salience scores at either baseline or follow up.

3.3.1.6 Longitudinal effects of four-week antipsychotic treatment on rCBF

To explore the effects of antipsychotic medications on cerebral perfusion, changes from baseline to follow up were identified using an exploratory voxel-wide search performed with $p<0.01$, uncorrected. Clusters identified were then explored for suprathreshold statistics accepted at $p<0.05$ and FWE-corrected for multiple comparisons. For completeness, and to ensure that rCBF measurements were stable

over time in my healthy control sample, I also implemented longitudinal analyses of healthy controls over four weeks to assess for rCBF changes across this period without any intervention.

As reported above, extracted global rCBF values showed that patients had a mean of 319.77 ml blood/100g tissue/minute (S.D. 72.29) at baseline, and a mean of 296.64 ml blood/100g tissue/minute (S.D. 60.21) at follow up. This change represented a significant decrease in global rCBF over four weeks treatment ($t(18)=2.22$, $p=0.039$). Healthy controls had a mean of 312.87 ml blood/100g tissue/minute (S.D. 77.80) at baseline and a mean of 316.65 ml blood/100g tissue/minute (S.D. 72.22) at follow up. There was no significant change in global rCBF in healthy controls across four weeks ($t(21)=-0.57$, $p=0.58$).

Table 54 and Figure 33 show clusters of significantly altered rCBF in patients following four-week antipsychotic treatment.

Table 54: *Areas of significant rCBF changes in patients after 4 weeks treatment*

Coordinates are shown in MNI space. P values have been FWE-corrected for multiple comparisons across the whole brain. Values for cluster-level significance are reported.

Brain area	L/R	x	y	z	t	K_E	P value
Follow up > Baseline							
Superior parietal lobe	L	-24	-54	58	4.28	2753	0.001

Patients at follow up relative to baseline showed one cluster of significantly increased rCBF. This cluster was centred on the left superior parietal lobe and extended into left frontal lobe. There were no regions of significantly decreased rCBF.

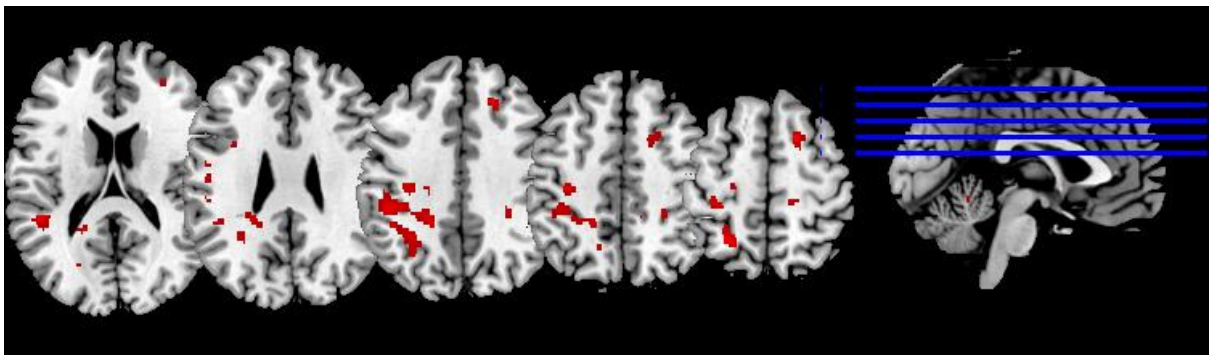

Figure 33: Perfusion differences at follow up compared with baseline in patients following four weeks' treatment

In patients, four weeks of treatment led to increased perfusion (red) in the parietal lobe.

3.3.1.7 Region of interest analyses

ROIs were examined to explore a priori hypotheses of expected differences between patients and healthy controls in the hippocampus, caudate, and putamen at baseline and follow up. There were no significant differences between patients and healthy controls in any of these regions, at either baseline or follow up.

To specifically assess my proposed hypotheses regarding alterations in rCBF following treatment, a ROI analysis was also executed to explore changes in patients in striatal, frontal, and hippocampal perfusion. There were no significant increases or decreases in rCBF in any of the ROIs in patients over the four weeks.

3.3.2 Resting CBF in responders and non-responders

In these sections, I present rCBF data for patients in relation to response to treatment at four and 12 weeks, to assess the associations of this measure with short- and longer-term treatment response. These analyses will reveal any potential differences in rCBF patterns in responders and non-responders at both baseline and follow, which could aid prediction of treatment response. I also explore the longitudinal changes seen in responders and non-responders, which will reveal whether antipsychotics affect rCBF in these groups differently.

3.3.2.1 Treatment response at four weeks

Treatment response in the following analyses was determined at four weeks and defined according to the Andreasen (2005) criteria.

3.3.2.1.1 Cross-sectional comparisons of baseline global rCBF in four-week responders and non-responders

Extracted global rCBF values showed that four-week responders had a mean of 315.10 ml blood/100g tissue/minute (S.D. 66.25) at baseline, whilst four-week non-responders had a mean of 313.08 ml blood/100g tissue/minute (S.D. 94.59). These values were not significantly different (n.s., $p>0.05$). Global rCBF values in responders and non-responders also did not differ significantly from those of healthy controls at baseline (n.s., $p>0.05$).

3.3.2.1.2 Cross-sectional comparisons of baseline rCBF in four-week responders and non-responders

a) Four-week responders versus non-responders

Figure 34 and Table 55 show clusters of significantly different rCBF in four-week responders compared with non-responders at baseline.

Table 55: *Areas of significant baseline rCBF differences in four-week responders and non-responders*

Coordinates are shown in MNI space. P values have been FWE-corrected for multiple comparisons across the whole brain. Values for cluster-level significance are reported.

Brain area	L/R	x	y	z	t	K_E	P value
Responders > Non-responders							
Posterior cerebellum	L	-16	-80	-46	5.59	2505	<0.0001
Thalamus	L	-10	-26	14	3.68	1840	0.021

At baseline, there were two clusters of significantly greater rCBF in four-week responders compared with non-responders. The first cluster was centred on the bilateral posterior cerebellum. The second cluster was centred on the bilateral thalamus, extending into left parahippocampal regions (BA30). There were no regions of lower rCBF in responders compared with non-responders.

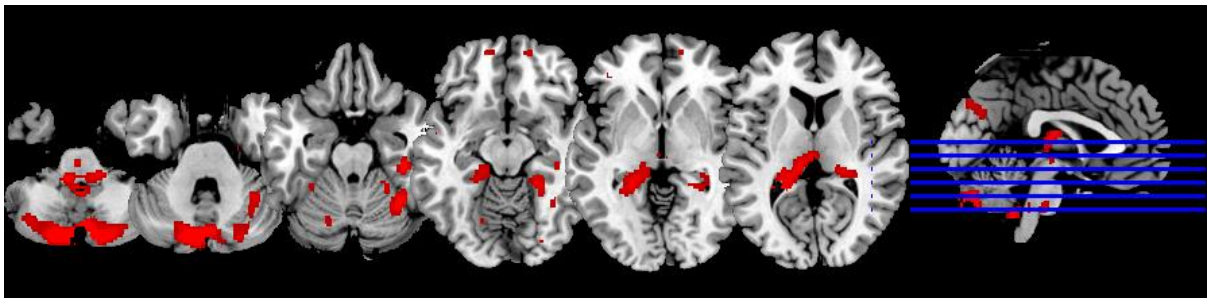

Figure 34: Baseline perfusion differences in four-week responders and non-responders

Higher resting perfusion (red) in responders compared with non-responders was observed at baseline in the cerebellum and thalamus.

b) Four-week responders versus healthy controls

Figure 35 and Table 56 show clusters of significantly different rCBF in four-week responders compared with healthy controls at baseline.

Table 56: *Areas of significant rCBF differences in four-week responders and healthy controls at baseline*

Coordinates are shown in MNI space. P values have been FWE-corrected for multiple comparisons across the whole brain. Values for cluster-level significance are reported.

Brain area	L/R	x	y	z	t	K_E	P value
Responders < Healthy controls							
Parietal (angular gyrus)	L	-46	-68	30	5.80	1610	0.04

Before treatment, four-week responders had lower rCBF than healthy controls in one significant cluster. This cluster was centred on the left parietal lobe (angular gyrus), extending into the left middle temporal gyrus and inferior temporal lobe. There were no regions of greater rCBF in responders compared with healthy controls at baseline.

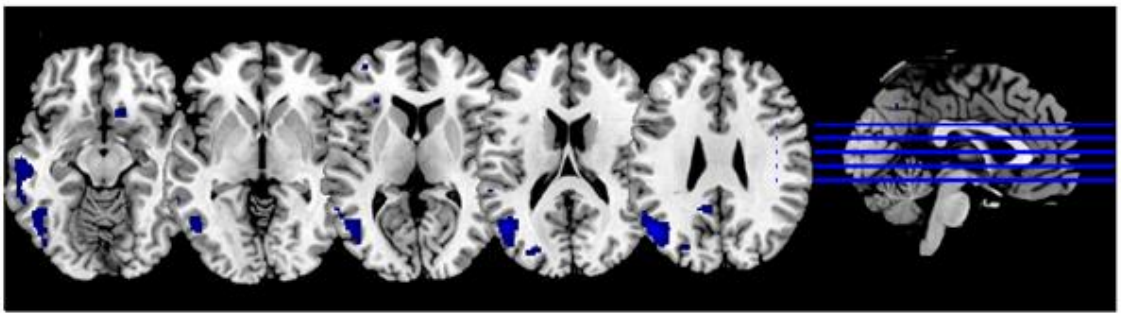

Figure 35: *Perfusion differences between four-week responders and healthy controls at baseline*

Lower resting perfusion (blue) in responders compared with healthy controls before treatment was commenced seen in the parietal lobe (angular gyrus)

c) Four-week non-responders versus healthy controls

Figure 36 and Table 57 show clusters of significantly different rCBF in four-week non-responders compared with healthy controls at baseline.

Table 57: *Areas of significant rCBF differences in four-week non-responders and healthy controls at baseline*

Coordinates are shown in MNI space. P values have been FWE-corrected for multiple comparisons across the whole brain. Values for cluster-level significance are reported.

Brain area	L/R	x	y	z	t	K_E	P value
Non-responders < Healthy controls							
Inferior parietal lobe	L	-48	-40	42	4.72	3758	<0.0001
Precuneus	L	-6	-56	36	3.95	8181	<0.0001

Four-week non-responders had lower rCBF than healthy controls in two significant clusters. The first cluster was centred on left inferior parietal lobe, extending into the supramarginal gyrus and the left angular gyrus of the temporal lobe. The second cluster was centred on the left precuneus of the parietal lobe, extending into the left thalamus. There were no regions of higher perfusion in non-responders compared with healthy controls at baseline.

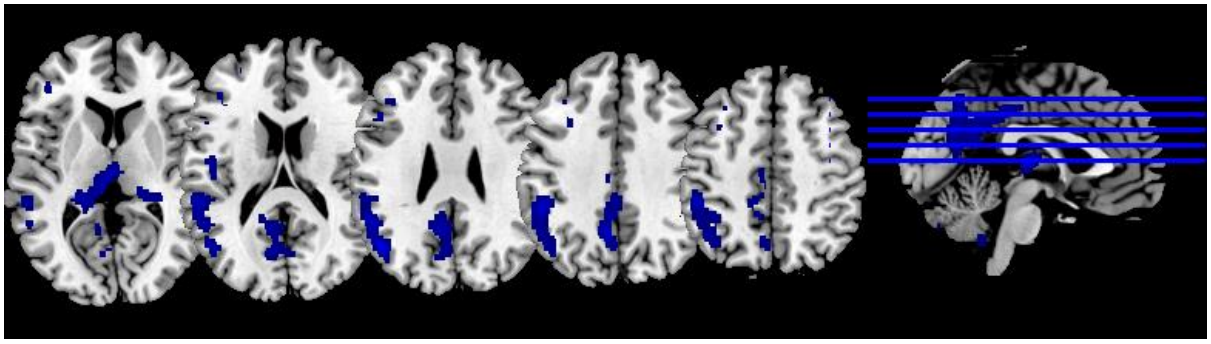

Figure 36: *Perfusion differences between four-week non-responders and healthy controls at baseline*

Lower resting perfusion (blue) in non-responders compared with healthy controls before treatment was commenced seen in the inferior parietal lobe and the precuneus.

3.3.2.1.3 Cross-sectional comparisons of follow up global rCBF in four-week responders and non-responders

At follow up, there was also no difference in global rCBF (n.s., $p>0.05$), with four-week responders having a mean of 313.69 ml blood/100g tissue/minute (S.D. 51.12) and four-week non-responders having a mean of 273.21 ml blood/100g tissue/minute (S.D. 67.12). Global rCBF values in four-week responders and non-responders did not differ significantly from those of healthy controls at either baseline or follow up (all n.s., $p>0.05$).

3.3.2.1.4 Cross-sectional comparisons of follow up rCBF in four-week responders and non-responders

a) Four-week responders versus non-responders

At follow-up, there were no longer any regions of greater or lower rCBF in four-week responders compared with non-responders.

b) Four-week responders versus healthy controls

Figure 37 and Table 58 show clusters of significantly different rCBF in four-week responders compared with healthy controls at baseline.

Table 58: *Areas of significant follow up rCBF differences in four-week responders and healthy controls*

Coordinates are shown in MNI space. P values have been FWE-corrected for multiple comparisons across the whole brain. Values for cluster-level significance are reported.

Brain area	L/R	x	y	z	t	K_E	P value
Responders > Healthy controls							
Superior temporal lobe	L	-44	-4	-14	4.36	3092	0.001

Four-week responders had greater perfusion than healthy controls in one cluster, centred in the left superior temporal lobe and extending into the left lateral globus pallidus. There were no regions of lower rCBF in four-week responders compared with healthy controls at follow up.

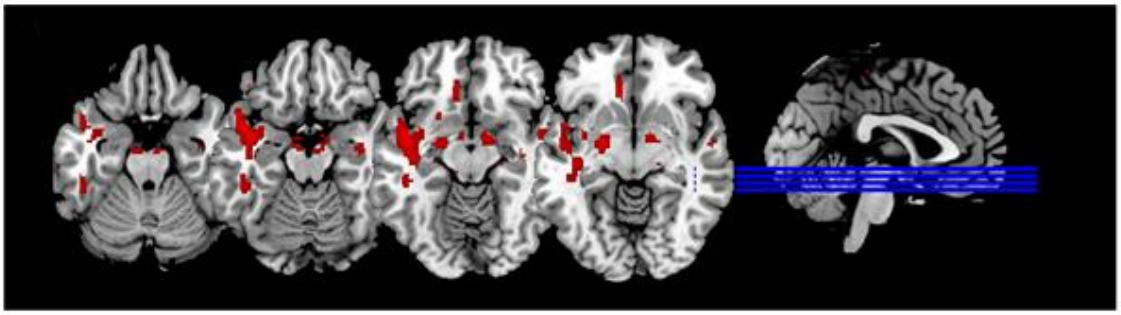

Figure 37: *Perfusion differences between four-week responders and healthy controls at follow up*

Higher resting perfusion (red) in responders compared with healthy controls after treatment was commenced seen in the superior temporal lobe.

c) Four-week non-responders versus healthy controls

There were no regions of either higher or lower perfusion in four-week non-responders compared with healthy controls at follow up.

d) Extracted values

It is interesting that the cluster of greater perfusion in responders included the globus pallidus (which has previously been shown to be altered by antipsychotic treatment). Furthermore, the higher perfusion was seen only in responders and not in non-responders, suggesting that it is effective antipsychotic treatment that leads to changes in this structure. I extracted mean perfusion values for this cluster in four-week responders (mean: 368.72 ml blood/100g tissue/minute), four-week non-responders (302.97 ml blood/100g tissue/minute), and healthy controls (321.13 ml blood/100g tissue/minute).

These values suggest that perfusion in this region for non-responders was lowest and close to healthy control values, whilst responders had greater perfusion in this regions than both the other groups. However, there were no significant differences between responders and non-responders ($t(17)=1.96$, $p=0.067$), responders and healthy

controls (t(27)=1.78, p=0.087), or non-responders and healthy controls (t(24)=-0.59, p=0.56).

3.3.2.1.5 Correlations between rCBF and clinical measures in four-week responders and non-responders

Significant clusters from the comparison of responders and non-responders were extracted and correlational analyses with clinical measures were conducted to explore relationships between the differences in these regions and clinical changes in patients.

(i) PANSS scores

Lower perfusion at baseline in the thalamus was negatively correlated with scores on the positive subscale of the PANSS at follow up (r=-0.454, p=0.026), indicating that those with continued higher positive symptom severity after treatment had lower thalamic perfusion at baseline. There were no other significant correlations between any of the suprathreshold clusters and PANSS scores at either baseline or follow up.

(ii) CGI

There were no significant correlations between clusters in which rCBF was significantly different in four-week responders compared with non-responders and CGI scores at either baseline or follow up.

(iii) PSP

There were no significant correlations between clusters in which rCBF was significantly different in four-week responders compared with non-responders and PSP scores at either baseline or follow up.

(iv) CDSS

There were no significant correlations between clusters in which rCBF was significantly different in four-week responders compared with non-responders and CDSS at either baseline or follow up.

(v) Antipsychotic dose

There were no significant correlations between clusters in which rCBF was significantly different in four-week responders compared with non-responders and antipsychotic dose.

(vi) Salience attribution measures

There were no significant correlations between clusters in which rCBF was significantly different in four-week responders compared with non-responders and salience scores at either baseline or follow up.

3.3.2.1.6 Longitudinal effects of four-week antipsychotic treatment on rCBF in four-week responders

Extracted global rCBF values showed that four-week responders had a mean global value of 315.10 ml blood/100g tissue/minute (S.D. 66.25) at baseline and a mean of 313.69 ml blood/100g tissue/minute (S.D. 15.41) at follow up. These values were not significantly different ($t(10)=0.999$, $p=0.341$).

Table 59 and Figure 38 show clusters of significantly altered rCBF in four-week responders during four weeks of antipsychotic treatment.

Table 59: *Areas of significant altered rCBF in four-week responders after treatment*

Coordinates are shown in MNI space. P values have been FWE-corrected for multiple comparisons across the whole brain. Values for cluster-level significance are reported.

Brain area	L/R	x	y	z	t	K_E	P value
Baseline < follow up (with global covariate)							
Precentral gyrus	L	-32	-32	56	4.61	1442	0.005

Four-week responders at follow up relative to baseline showed one cluster of significantly increased rCBF. The significant cluster was centred on the left precentral gyrus (Brodmann area 4), and extended into the left sub-gyral and left superior parietal lobe. There were no regions of significantly decreased rCBF.

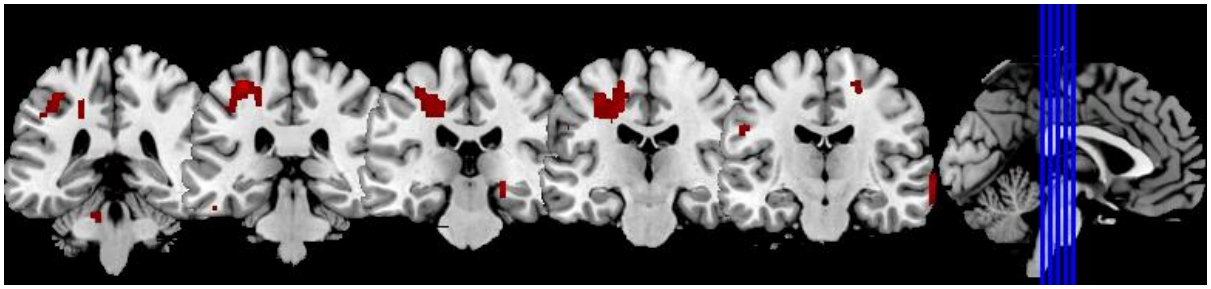

Figure 38: *Perfusion differences at four-week follow up compared with baseline in 4-week responders*

In responders, four weeks of treatment led to increased perfusion (red) in the left precentral gyrus.

3.3.2.1.7 Longitudinal effects of four-week antipsychotic treatment on rCBF in four-week non-responders

Four-week non-responders with baseline and follow up scans showed a significant decrease in rCBF with treatment (t(7)=2.45, p=0.044), with a baseline mean of 313.08

ml blood/100g tissue/minute (S.D. 94.59) and a follow-up mean of 273.21 ml blood/100g tissue/minute (S.D. 67.12).

There were no regions of either increased or decreased rCBF in four-week non-responders at follow up.

3.3.2.2 Treatment response at 12 weeks

Treatment response for the following analyses was determined at 12 weeks, using the PPHS assessment.

3.3.2.2.1 Cross-sectional comparisons of baseline global rCBF in 12-week responders and non-responders

Extracted global rCBF values showed that at baseline 12-week responders had a mean of 320.58 ml blood/100g tissue/minute (S.D. 55.66), whilst non-responders had a mean of 314.72 ml blood/100g tissue/minute (S.D. 93.52). These values were not significantly different ($t(17)=0.171$, $p=0.866$).

3.3.2.2.2 Cross-sectional comparisons of baseline rCBF in 12-week responders and non-responders

a) Twelve-week responders versus non-responders

Table 60 and Figure 39 show clusters of significantly different rCBF in 12-week responders compared with non-responders at baseline.

Table 60: *Areas of significant baseline rCBF differences in 12-week responders and non-responders*

Coordinates are shown in MNI space. P values have been FWE-corrected for multiple comparisons across the whole brain. Values for cluster-level significance are reported.

Brain area	L/R	x	y	z	t	K_E	P value
Responders > Non-responders							
Precuneus	L	-6	-54	32	5.74	9435	<0.0001

At baseline, 12-week responders had greater rCBF than non-responders in one significant cluster. This cluster was centred on the left precuneus, extending into the thalamus. There were no regions of significantly lower rCBF in 12-week responders compared with non-responders.

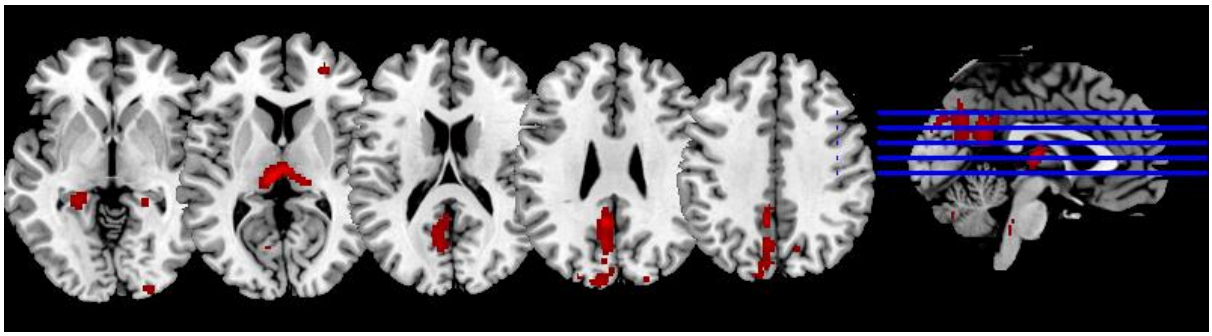

Figure 39: *Baseline perfusion differences in 12-week responders and non-responders*

Higher resting perfusion (red) in responders compared with non-responders is visible at baseline before treatment in a large cluster centred on the precuneus and extending into the thalamus.

b) Twelve-week responders versus healthy controls

At baseline, 12-week responders were compared with healthy controls to identify rCBF differences before treatment commenced in the patients. Table 61 and Figure 40 show regions of significantly different rCBF in responders compared with healthy controls at baseline.

Table 61: *Areas of significant baseline rCBF differences in 12-week responders and healthy controls*

Coordinates are shown in MNI space. P values have been FWE-corrected for multiple comparisons across the whole brain. Values for cluster-level significance are reported.

Brain area	L/R	x	y	z	t	K_E	P value
Responders < Healthy Controls							
Angular gyrus (parietal)	L	-46	-68	30	6.24	3352	<0.0001

Twelve-week responders had lower rCBF than healthy controls in one significant cluster. This cluster was centred on the angular gyrus of the left parietal lobe, extending into postcentral gyrus and supramarginal gyrus. There were no regions of significantly higher rCBF in 12-week responders compared with healthy controls at baseline.

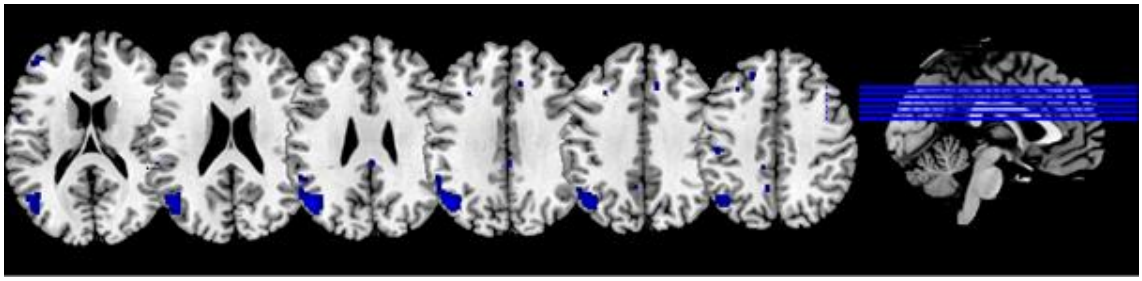

Figure 40: *Baseline* p*erfusion differences between 12-week responders and healthy controls*

Lower resting perfusion (blue) in responders compared with healthy controls before treatment was seen in the left angular gyrus of the parietal lobe.

c) Twelve-week non-responders versus healthy controls

At baseline, I also compared 12-week non-responders with healthy controls to identify rCBF differences before treatment commenced in these patients. Table 62 and Figure

41 show regions of significantly different rCBF in non-responders compared with healthy controls at baseline.

Table 62: *Areas of significant baseline rCBF differences in 12-week non-responders and healthy controls*

Coordinates are shown in MNI space. P values have been FWE-corrected for multiple comparisons across the whole brain. Values for cluster-level significance are reported.

Brain area	L/R	X	y	z	t	K_E	P value
Non-responders < Healthy Controls							
Inferior parietal lobe	L	-46	-66	26	6.36	13241	<0.0001
Cerebellum (declive)	R	24	-68	-26	3.82	1778	0.017

Twelve-week non-responders had lower rCBF than healthy controls in two significant clusters. The first cluster centred on the left inferior parietal lobe, extending into the precuneus. The second cluster centred on the declive of the cerebellum, extending into fusiform gyrus in the temporal lobe. There were no regions of significantly higher rCBF in 12-week non-responders compared with healthy controls at baseline.

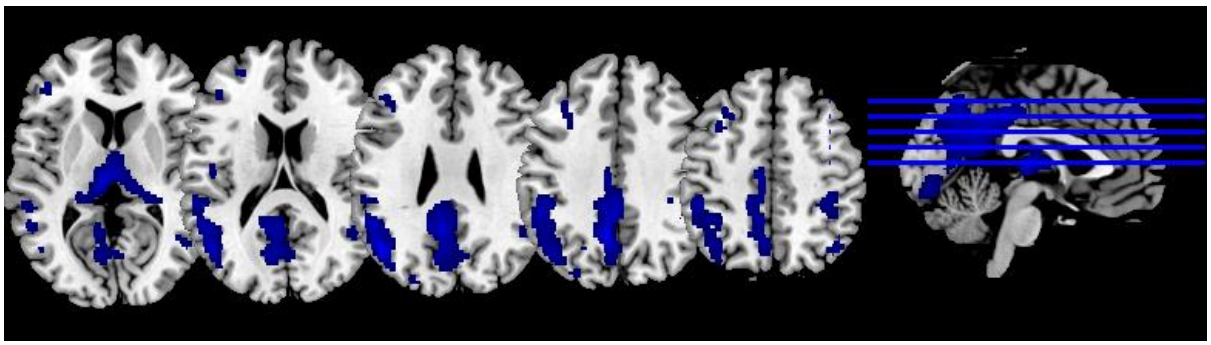

Figure 41: *Baseline* r*CBF differences between 12-week non-responders and healthy controls*

Lower resting perfusion (blue) in non-responders compared with healthy controls before treatment was seen in the left inferior parietal lobe and the cerebellum.

3.3.2.2.3 Cross-sectional comparisons of follow up global rCBF in 12-week responders and non-responders

At follow up, there was no difference in global rCBF (t(14)=0.491, p=0.631), with 12-week responders having a mean of 299.99 ml blood/100g tissue/minute (S.D. 73.51) and non-responders having a mean of 283.80 ml blood/100g tissue/minute (S.D. 57.38).

3.3.2.2.4 Cross-sectional comparisons of follow up rCBF in 12-week responders and non-responders

a) Twelve-week responders versus non-responders

At follow-up, there were no regions of significantly different rCBF between 12-week responders and non-responders.

b) Twelve-week responders versus healthy controls

At follow up, 12-week responders were compared with healthy controls to identify rCBF differences following four weeks of antipsychotic treatment in these patients. Table 63 and Figure 42 show regions of significantly different rCBF in 12-week responders compared with healthy controls at follow up.

Table 63: *Areas of significant follow up rCBF differences in 12-week responders and healthy controls*

Coordinates are shown in MNI space. P values have been FWE-corrected for multiple comparisons across the whole brain. Values for cluster-level significance are reported.

Brain area	L/R	x	y	z	t	K_E	P value
Responders > Healthy Controls							
Precuneus	L	-20	-54	30	5.2	1578	0.022
Temporal lobe	L	-40	-18	-12	4.26	1362	0.043

There were two significant clusters of greater rCBF in 12-week responders than in healthy controls. The first significant cluster was centred on the left precuneus, extending into the left postcentral gyrus. The second cluster was centred on the left temporal cortex subgyrally and extended into the left fusiform gyrus. There were no regions of significantly lower rCBF in 12-week responders compared with healthy controls at follow up.

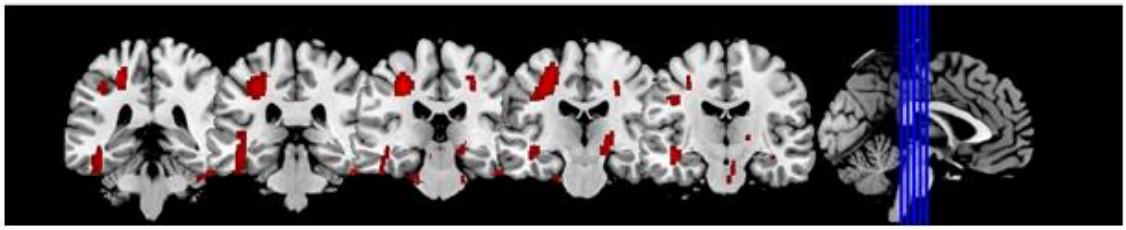

Figure 42: *Follow up* p*erfusion differences between 12-week responders and healthy controls*

Higher resting perfusion (red) in responders compared with healthy controls after treatment was seen in the left precuneus and the left temporal lobe.

c) Twelve-week non-responders versus healthy controls

At follow up, 12-week non-responders were compared with healthy controls to identify rCBF differences following four weeks of antipsychotic treatment in these patients. There were no regions of significantly different rCBF between 12-week non-responders and healthy controls at follow up.

3.3.2.2.5 Longitudinal effects of four-week antipsychotic treatment on rCBF in 12-week responders

Extracted global rCBF values showed that 12-week responders with baseline and follow up scans had a mean of 316.53 ml blood/100g tissue/minute (S.D. 59.55) at baseline and a mean of 299.99 ml blood/100g tissue/minute (S.D. 73.51) at follow up. These values were not significantly different ($t(7)=1.30$, $p=0.24$).

Table 64 and Figure 43 show regions of significantly altered rCBF in 12-week responders after four weeks of antipsychotic treatment.

Table 64: *Areas of significant altered rCBF in 12-week responders after four weeks of treatment*

Coordinates are shown in MNI space. P values have been FWE-corrected for multiple comparisons across the whole brain. Values for cluster-level significance are reported.

Brain area	L/R	x	y	z	t	K_E	P value
Baseline > follow up							
Parahippocampal gyrus	L	-24	-42	2	17.11	815	0.015
Baseline < follow up							
Parietal lobe	L	-24	-28	50	13.04	2192	<0.0001

In 12-week responders, there was one significant cluster of decreased rCBF at follow up. This centred on the left parahippocampal gyrus. There was also a significant cluster of increased rCBF, centred in the left parietal lobe and extending into the precentral gyrus and temporal lobe.

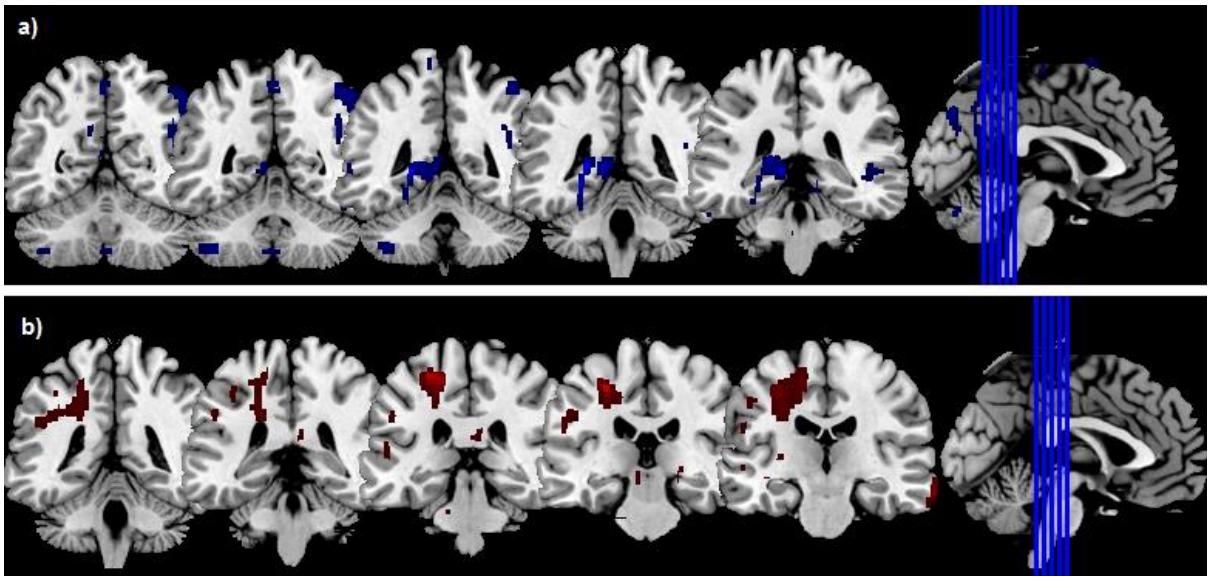

Figure 43: *a) Perfusion decreases and b) increases across 4 weeks of treatment in 12-week responders*

a) Decreased resting perfusion (blue) in 12-week responders was seen in the parahippocampal gyrus; and b) increased resting perfusion (red) in 12-week responders was seen in the left parietal lobe.

3.3.2.2.6 Longitudinal effects of four-week antipsychotic treatment on rCBF in 12-week non-responders

Twelve-week non-responders with baseline and follow up scans had a mean of 314.72 ml blood/100g tissue/minute (S.D. 93.52) at baseline and a mean of 283.80 ml blood/100g tissue/minute (S.D. 57.38) at follow up. These values were not significantly different (t(7)=1.87, p=0.10).

Table 65 and Figure 44 shows regions of significantly altered rCBF in 12-week non-responders after four weeks of antipsychotic treatment.

Table 65: *Areas of significantly altered rCBF in 12-week non-responders after four weeks of treatment*

Coordinates are shown in MNI space. P values have been FWE-corrected for multiple comparisons across the whole brain. Values for cluster-level significance are reported.

Brain area	L/R	x	y	z	t	K_E	P value
Baseline < follow up							
Post-central gyrus (parietal)	R	14	-40	68	10.86	923	0.014

In 12-week non-responders, there was one significant cluster of increased rCBF at follow up. This was centred in the right post-central gyrus, extending into the precuneus. There were no regions of significantly decreased rCBF in 12-week non-responders.

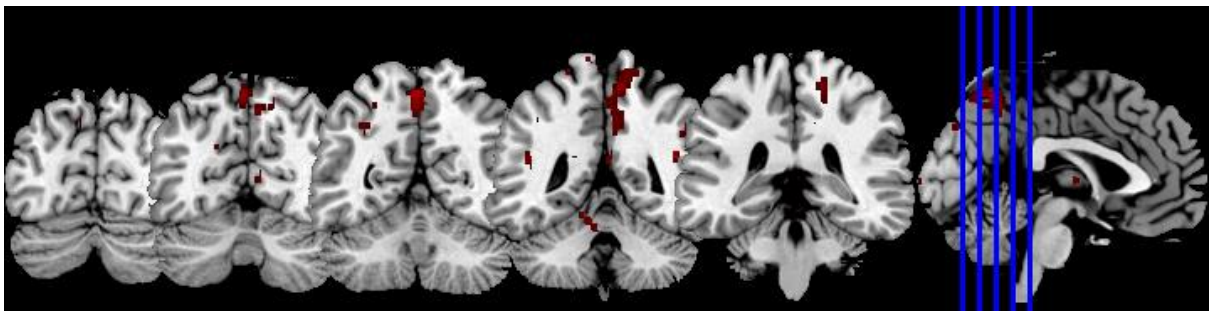

Figure 44 *Resting rCBF increases across four weeks of treatment in 12-week non-responders*

Increased resting perfusion (red) in 12-week non-responders was seen in the left postcentral gyrus of the parietal lobe.

3.3.3 Chapter summary

In this chapter, I have described the effects of antipsychotic treatment on cerebral blood flow in patients with FEP. Furthermore, I have explored the relationship of rCBF at baseline and after four-week treatment with treatment response as assessed at four or 12 weeks.

Overall, patients showed differences from healthy controls both before and after treatment. Before treatment, patients had lower resting perfusion in temporal and parietal regions compared with healthy controls. Lower perfusion in the middle temporal gyrus was related to higher baseline CDSS scores of depression. After four weeks of treatment, patients had higher perfusion in the left superior temporal gyrus compared with healthy controls, and this was positively correlated with antipsychotic dose. These results suggest that patients already differ from healthy controls before they are treated, and that antipsychotic treatment alters rCBF.

When treatment response was considered, I observed differences in the perfusion patterns of responders and non-responders. At baseline, responders had higher cerebellar and thalamic rCBF than non-responders. Furthermore, higher baseline thalamic rCBF was positively correlated with lower positive PANSS scores at follow up, suggesting an association between thalamic perfusion and response. Both responders

and non-responders showed lower perfusion in parietal regions compared with healthy controls at baseline, but only responders had higher perfusion in the superior temporal gyrus at follow up. Antipsychotic medication led to increased rCBF in the precentral gyrus of responders. However, there appeared to be no changes in rCBF in any region with treatment in non-responders. The presence of differences evident before treatment, and which are associated with response to treatment four or 12 weeks later suggests that rCBF may have predictive value.

I investigated three ROIs, in relation to my specific hypotheses, investigating rCBF in the hippocampus, caudate, and putamen. No significant differences were found in any of these regions to support the hypotheses.

The results in this chapter suggest that antipsychotic medication alters rCBF in patients with FEP and that the changes seen depend on response to treatment.

4. DISCUSSION

In this final chapter, I discuss my findings. Initially, I will summarise the main findings of each results chapter in turn, discussing the results within the context of existing literature, and considering potential mechanisms and explanations for my findings. I will also consider limitations of the study and the implications for the field of schizophrenia. Finally, I will present my main conclusions and potential future directions for the field.

4.1 Summary and interpretation of the findings

In chapters 3.1, 3.2, and 3.3, I report the differences between patients and healthy controls on clinical, behavioural, and neurophysiological measures. I also investigated the longitudinal effects of antipsychotic medication on these measures. I further investigated associations between the effects observed and whether patients showed a good or poor response to treatment at four and 12 weeks. The main findings are summarised below:

- In general, amisulpride led to improvements in psychotic symptomatology for the patient group. At an individual level, not all patients improved, with 17 (68%) showing a good response and 8 (32%) showing a poor response to treatment. Non-response was associated with a greater severity of illness at baseline and a longer duration of untreated psychosis (DUP) at baseline.
- Overall, patients significantly differed from healthy controls only in terms of explicit adaptive salience, both at baseline and follow up. Furthermore, there were no significant changes in patients with treatment in any salience measures. However, within the patient sample, altered salience attribution appeared to be related to treatment response. A good response was associated with higher implicit adaptive salience scores at baseline. Successful treatment also appeared to be associated with significant decreases in implicit aberrant

salience, which was seen in responders but not non-responders. Finally, delusions were associated with lower levels of implicit adaptive salience at baseline.

- Salience processing was associated with activation in frontal and temporal regions, with a wider range of regions activated in healthy controls. The patient group as a whole did not differ from healthy controls at either baseline or follow up in activation. There were differences in neural activation patterns of responders and non-responders. There was greater activation in the insula and midbrain during adaptive salience in four-week responders than in non-responders before and after treatment, respectively. Responders differed little from healthy controls, showing differences during presentation of outcome at follow up only, in the middle temporal lobe. Non-responders differed from healthy controls at both time points, with lower activation in the cerebellum and brainstem. Longer-term response was also associated with differences in brain activation, with a good response associated with higher baseline activation in superior temporal and middle occipital lobes during adaptive salience. There were no differences in neural activation during aberrant salience processing at any time point between any of the groups.
- In terms of brain perfusion, before treatment, the whole patient group showed hypoperfusion in temporal and parietal regions compared with healthy controls. At follow up, patients compared with healthy controls had higher perfusion in the superior temporal gyrus extending into the globus pallidus, and this was positively correlated with antipsychotic dose. There were differences in perfusion patterns of responders and non-responders, with responders showing higher cerebellar and thalamic rCBF at baseline compared with non-responders. Furthermore, higher baseline thalamic rCBF was positively correlated with lower positive PANSS scores at follow up, suggesting an association between thalamic perfusion and response. Both responders and non-responders showed lower perfusion in parietal regions compared with

healthy controls at baseline, but only responders had higher perfusion in the superior temporal gyrus at follow up. Antipsychotic medication led to increased rCBF in the precentral gyrus of responders. However, there appeared to be no changes in rCBF in any region with treatment in non-responders.

4.1.1 The effects of amisulpride on clinical, behavioural, and neurobiological measures.

Whilst our understanding of the pharmacodynamic effects of antipsychotic medications has improved, we still lack a clear understanding of the short and long term effects of antipsychotic medications on the brain. However, increasing evidence suggests that structural and functional brain changes observed in psychosis are partly a result of antipsychotic treatment (Navari and Dazzan, 2009; Ho et al., 2011; Davis et al., 2005; Vita and De Peri, 2007; Goozee et al., 2014).

In this project, I investigated the effect of amisulpride, a second generation antipsychotic (SGA), on various clinical, behavioural, and neurobiological measures, in a relatively homogeneous sample of patients with first episode psychosis (FEP). These patients were either antipsychotic-naïve or minimally treated, and had been ill for less than two years. They therefore provide an advantage over samples in previous studies, which have recruited heterogeneous groups of patients, often with previous exposure to antipsychotic medication and a range of illness durations. These factors may further affect clinical, behavioural, and neurobiological factors related to schizophrenia. As such, my sample allows the interpretation of neurobiological factors, without the influence of previous treatments or illness chronicity. I found that the clinical, behavioural, and neurobiological measures I investigated were affected by four weeks of treatment with amisulpride. Below, I discuss these effects and consider their implications.

a) Clinical measures

Overall, amisulpride led to an improvement in patients' symptoms, with significant decreases in all PANSS subscales, apart from negative symptoms. These improvements were confirmed by the mean percent change scores on the PANSS, as well as changes in CGI and PSP ratings. The only measure not showing significant changes was CDSS, which was likely due to the fact that there were low levels of depressive symptoms in the sample to begin with. The improvement seen in symptoms is in line with findings from clinical trials. These have reported group-level efficacy of current antipsychotic medications, with superiority of SGAs, such as amisulpride, over first generation antipsychotics (FGA) (Leucht et al., 2009). Whilst patients tended to get better, in my sample there was no significant improvement in negative symptoms following treatment with amisulpride. Whilst there has been some debate surrounding the efficacy of current treatments to improve negative and cognitive symptoms in schizophrenia, previous research has indicated a potential improvement in these domains with amisulpride treatment (Curran and Perry, 2001). This may not have been detected in our sample due to the sample size or due to our patients presenting with a low level of negative symptoms at baseline.

b) Behavioural measures of salience attribution

In 2003, Kapur proposed a framework to bridge the gap between the brain and the mind in psychosis, which suggested that dysfunctions in attributing importance to salient cues and neutral cues underlies psychotic symptoms such as hallucinations and delusions (Kapur, 2003). Furthermore, he proposed that the effect of antipsychotic medication on psychotic symptoms resulted from an effect on salience processing, mediated by the blockade of dopamine receptors. Investigating the effects of antipsychotics on salience processing thus provides a powerful way of testing the validity of the salience model of psychosis.

Initially, I investigated whether participants were able to use reward associations to guide how they responded (i.e., whether they responded more quickly to high-probability trials than low-probability trails). I found that this was the case at both baseline and four-week follow up. However, whilst healthy controls showed significant implicit adaptive salience (significantly different to zero) at both baseline and follow up, patients did not show significant levels of adaptive salience at baseline. However, after treatment they did show significant levels of adaptive salience. This suggests that antipsychotic treatment can ameliorate impaired reward learning in patients with psychosis, presumably through dopamine antagonism.

In the present project, patients had reduced explicit adaptive salience at baseline and follow up, but there were no differences in implicit (reaction time) scores. This suggests that patients were able to learn implicitly about the relationships between high-probability cues and reward, but were not aware or conscious of this learning. These findings are consistent with data from a previous study in patients with FEP, which found that they showed reduced explicit and implicit adaptive salience compared with healthy controls (Roiser et al., 2009). My findings extend these results, in that this difference was evident in patients who were medication naïve. Patients in the previous study had been treated with antipsychotic medication, and the reduction in adaptive salience was attributed to an effect of this on motivational salience, rather than an effect of the disorder itself (Roiser et al, 2009). Indeed, Kapur had originally proposed that adaptive salience was intact prior to treatment but diminished as a result of dopamine blockade following antipsychotic treatment (Kapur, 2003).

Longitudinal analyses of the whole patient group provided little evidence for a modulatory role of antipsychotics on salience attribution, as there were no significant changes in any salience measure in patients following treatment with amisulpride. There was a significant decrease in the number of premature errors made by patients with treatment, but this may have been due to increased familiarity with the task. However, healthy controls did not show a corresponding decrease in errors so this is

unlikely. Another possibility is that reduced errors reflected a reduction in distracting positive symptomatology following treatment.

In this sample, I found that patients with delusions had lower implicit adaptive salience scores at baseline than patients without delusions. It has been hypothesized that salience attribution when disrupted could play a particular role in the development of delusions. According to the aberrant salience hypothesis (Kapur, 2003), when there is disruption of normal salience attribution processes, neutral stimuli can be assigned unwarranted importance or salience, i.e., aberrant salience, and thus attract attention and influence behaviour inappropriately. It may be that delusions result from attempts to explain unusual experiences of heightened salience to neutral stimuli (Kapur, 2003). Consistent with this, Roiser and colleagues (2009) reported that delusional symptomatology was associated with higher levels of aberrant salience. There was a trend in my data for those with delusions at follow up to also have higher implicit aberrant salience scores but this was not significant. In contrast, delusions were related to lower levels of adaptive salience rather than higher levels of aberrant salience.

c) Neural activation during salience attribution measured using fMRI

This study also investigated salience attribution within the context of the salience attribution theory at the level of brain activation. I analysed neural activation using fMRI BOLD during salience attribution, performing contrasts that represent adaptive and aberrant salience, as well as the outcome of trials.

At baseline, I investigated activation associated with salience processing in healthy controls and patients, separately. Previous studies have reported activation associated with adaptive salience (i.e., when individuals differentiate between high and low probability cues) in the midbrain, ventral tegmental area, medial dorsal thalamus, ventral striatum, and prefrontal cortex of healthy controls (Roiser et al., 2010). I found that adaptive salience at baseline was associated with activation in the superior temporal gyrus (STG) of healthy controls . This region is not often implicated in reward

or salience processing, but cues associated with adaptive salience have been shown to elicit greater activation in the STG than other cues in healthy controls (Roiser et al., 2010) and individuals with at-risk mental state (ARMS) (Roiser et al., 2013). In patients, I found that no regions were significantly activated during adaptive salience processing at baseline. At follow up, activation associated with adaptive salience was found in similar regions as at baseline, with the superior temporal gyrus most consistently activated in both patients and healthy controls. It is possible that the lack of activation found at baseline could be due to my use of a single block during the SAT and fewer trials than in previous studies. This may have resulted in a lack of power to detect the activation. Nonetheless, further imaging studies of salience attribution processes could confirm the networks of regions activated during both adaptive and aberrant salience attribution and their contributions to salience processing.

In this study, there were no significant clusters of neural activation changes associated with aberrant salience. Previous studies have found differential dorsolateral PFC and medial temporal gyrus (MTG) activation to cues with identical reward properties. The relationship between these regions and salience processing remains speculative. Roiser and colleagues (2010) suggested that their role in aberrant salience may be related to their previously reported role in signalling uncertainty during reward learning. However, what is important is that where aberrant salience was present, and identically rewarded cues were responded to as if they were differentially rewarded, neural activation in the dorsolateral PFC and MTG also reflected this aberrant attribution of salience. When participants responded neutrally to cues that were equally rewarded (i.e. did not show aberrant salience) this activation was not seen. The presence of activation in any region associated with the erroneous attribution of salience to cues (treating neutral cues as if they were differentially rewarded) was not seen in our participants. This may have been due to generally low levels of aberrant salience in our groups. Alternatively, this may have been due to a lack of power resulting from fewer trials during the SAT (as described above).

When the patients were compared with healthy controls, no significant differences were found at either baseline or follow up in adaptive salience activation. Whilst this is not the first study to report a lack of difference between patients and healthy controls (Simon et al., 2010), most studies in patients with chronic schizophrenia have reported reduced striatal and frontal activation during reward and salience processing in patients compared with healthy controls (Koch et al., 2010; Walter et al., 2009; Simon et al., 2010; Waltz et al., 2010; Diaconescu et al., 2011; Gradin et al., 2011/2013; Dowd and Barch, 2012; da Silva Alves et al., 2013). Most of the patients in these studies had already been treated with antipsychotics, and had been ill for longer than the participants in my study. It is possible that antipsychotics modulate salience processing and its underlying neural function. Furthermore, there may also be changes in salience attribution as the illness progresses (including effects of changes in general cognition). However, studies in patients with FEP have also reported functional abnormalities in various regions, for example failure to adequately activate midbrain, striatal, and limbic regions in response to high-probability cues (Murray et al., 2008). Nonetheless, our patients did not differ from healthy controls either at baseline or follow up. This is inconsistent with a recent study showing lower adaptive salience responses in FEP compared with healthy controls in the right insula (Smieskova et al., 2015). However, unlike my sample, the patients in this study were medicated. We also did not find any differences between groups in terms of aberrant salience activation. This finding is consistent with a recent study that compared ARMS, FEP and healthy controls on the SAT using fMRI, finding no differences in aberrant salience measures (Smieskova et al., 2015).

When considering the longitudinal effects of antipsychotics on brain activation during salience processing, I found no effect of treatment in our patients. Again, this is not consistent with previous studies, although only two have considered the effects of antipsychotics prospectively in patients, and both used the monetary incentive delay (MID) task rather than the SAT (Schlagenhauf et al., 2008b; Nielsen et al., 2012). Only

the patients in one of these studies were medication-naïve before entering the study (Nielsen et al., 2012), whereas patients in the other study were medicated with FGA and then switched to olanzapine (Schlagenhauf et al., 2008b). Both these studies found decreased activation in the ventral striatum of patients during reward anticipation, which normalised after treatment, such that patients no longer differed from healthy controls. It is possible that the MID task and SAT are measuring fundamentally different concepts, and as such differences in findings should be expected with them. This highlights the question of what precisely is being measured when we discuss adaptive and aberrant salience. Whether these are valid cognitive concepts that reflect real-world cognitive processes and how they relate to other reward-learning concepts is not entirely clear.

The lack of difference found in my study could be explained in several ways. It is possible that the short period of treatment between scans (four weeks) was not long enough for changes to become apparent. However, antipsychotics have been shown to have immediate effects on brain function, even after a single dose (e.g. Handley et al., 2013) and previous studies have used similar treatment periods of between four and six weeks (e.g. Honey et al., 1999, Schlagenhauf et al., 2008a/b, 2010). A lack of difference may result from the characteristics of the patient sample. As I recruited only antipsychotic-naïve FEP patients who had not been compelled to receive clinical care or admitted to hospital, whereas previous studies have included patients who had already been treated, who had been admitted to hospital, or who were being treated on a compulsory basis. It is thus possible that the studies involved different types of patient, and those in my study were less severely ill than in the previous samples. Similarly, there were few differences in behavioural measures of salience attribution when the entire patient group was compared with healthy controls (see above). The only difference found was in explicit adaptive salience, i.e., the ability of a patient to verbalise the relationship between high-probability cues and reward. Given the lack of

neural differences, it is possible that this behavioural difference is due to indirect effects of the illness on learning or cognition.

However, the most parsimonious explanation for the lack of striking differences between the overall patient sample and controls is that the findings are closely related to the effect of antipsychotic medication. Pooling all patients together may have constituted a heterogeneous group which made it harder to detect significant findings. Stratifying patients according to treatment response may have generated subgroups that were more biologically homogenous, increasing the likelihood of detecting correlates of salience abnormalities.

d) Resting CBF measured using cASL

Resting CBF is a measure of basal brain activity that is potentially important in understanding the effects of antipsychotics on the brain. It has been related to antipsychotic use (Pinkham et al., 2011) and the regions affected show overlap with those reported elsewhere as altered in psychosis (Miller et al., 2001; Lahti et al., 2003). Changes following antipsychotic treatment are seen immediately, within a few hours of single-dose administration (Handley et al., 2012), but in this project, longer term administration across four weeks was investigated.

In this project, patients with FEP showed differences in rCBF compared with healthy controls before they were treated with an antipsychotic medication. A limited number of studies in antipsychotic-naïve or unmedicated patients have been conducted. Such studies suggest the presence of perfusion differences in the frontal cortex, basal ganglia, and temporal regions (e.g. Scheef et al., 2010; Kim et al., 2000; Andreasen et al., 1997). In my sample, I found differences between patients and healthy controls before treatment in the temporal and parietal lobes. Furthermore, one cluster of decreased perfusion extended into the frontal lobe. However, I did not replicate previously reported differences in the basal ganglia. I discuss potential reasons for the differences I found and how they may relate to disease pathology below.

There are a number of potential explanations as to why there may be inconsistencies between my results and those of previous studies. A major potential source of variability is sample heterogeneity. As already stated above, a number of variables that may affect brain perfusion vary between different studies and often vary to a large extent within a study. These include illness chronicity and illness severity, as well as previous and current antipsychotic exposure. Indeed, the samples of many previous studies reporting perfusion abnormalities in patients with schizophrenia have comprised individuals who are more chronically ill and have been previously medicated. There is increasing evidence for a modulatory effect of antipsychotic medication on brain perfusion (Goozee et al., 2014). As such, it is difficult when using samples including those who have been previously medicated to disentangle where perfusion abnormalities are primary to the disease pathophysiology or reflect changes resulting from treatment.

The importance of antipsychotic exposure has been highlighted by Vita and colleagues (1995). They conducted a perfusion study in which patients were separated according to previous antipsychotic exposure. When they compared nine antipsychotic-naïve patients with healthy controls, they found hypoperfusion in frontal, temporal, and subcortical regions (thalamus, caudate, and putamen). However, the eight antipsychotic-free patients (who had undergone a minimum three-week washout) did not differ from healthy controls. These results suggest that antipsychotic medications have a modulatory effect on rCBF. Furthermore, this effect can be long-lasting, even after the withdrawal of medication. In another study, it was found that rCBF in the basal ganglia and temporal lobes was inversely related to the duration of washout (Ebmeier et al., 1993). Thus, whilst I did not find alterations in the basal ganglia, this may be related to the characteristics of my sample, such as their lack of previous antipsychotic exposure. These characteristics allow us to more confidently assert that the differences observed are primary to the disease pathophysiology, rather than secondary to other factors. Samples which include patients with a range of illness durations and previous

treatments are difficult to interpret. If we are to understand the effects of antipsychotics on the brain and how they modulate the pathophysiology underlying psychotic illness, more research is required in samples that are uncontaminated by previous antipsychotic use.

One finding from previous studies that was replicated in this project was altered temporal perfusion, particularly in the left hemisphere, of patients with psychosis. At baseline, patients had lower perfusion in the middle temporal gyrus. A large body of research implicates temporal abnormalities in psychotic illness, with alterations in structure, function, and perfusion. A number of studies of rCBF in schizophrenia have found decreased perfusion in the temporal cortex (Ebmeier et al., 1993; Catafau et al., 1994; Steinberg et al., 1995; Vita et al., 1995; Andreasen et al., 1997; Kim et al., 2000; Scheef et al., 2010). Differences in the temporal lobes were still observed at follow up, after four weeks of treatment. However, at this point, patients had higher rCBF in the superior temporal lobe. Higher perfusion in this region was also associated with higher antipsychotic dose.

The temporal lobe plays a role in auditory processing and so has previously been implicated in the development of hallucinatory symptoms of psychosis (Shenton et al., 2001). In particular, it is possible that hallucinations may derive from dysfunction in normal auditory and language functions, which are supported by temporal cortex activity. It is therefore particularly interesting that the differences seen are invariably in the left hemisphere. Lateralisation of language to the left side of the brain has been well-established since early work by Broca (Broca, 1865; Hécaen et al., 1981). The temporal lobe has extensive interconnections with the frontal lobe, another area often associated with abnormalities in schizophrenia. Indeed, the clusters of decreased perfusion found in my study also extended into the frontal lobe. It is likely that brain alterations in schizophrenia are diffusely distributed across the brain and will affect networks, rather than resembling localised lesions or isolated regions of altered function (Mourao-Miranda et al., 2012).

Temporal lobe deficits in patients with psychosis have previously been reported in structural studies, and these may be affected by antipsychotics (Dazzan et al., 2005). However, few studies have explored associations between temporal perfusion and antipsychotic medications. Where this has been investigated, results have been mixed. Some have reported no changes in temporal lobe perfusion following long-term or single dose antipsychotic treatment (Yildiz et al 2000; Miller et al. 1997; Vaiva et al., 2002; Gonul et al., 2004). Others have suggested decreased metabolism or blood flow in this region after treatment (Lahti et al., 2003; Lahti et al., 2009; Bartlett et al., 1998). Conflicting results may result from differences in the length of time between administration of a drug and scanning and the type of antipsychotic prescribed. For example, haloperidol (a FGA) has been associated with decreased temporal blood flow, whilst olanzapine (a SGA) was associated with increased temporal blood flow in the same participants (Lahti et al., 2005). The same group reported decreased temporal rCBF after one week of treatment with olanzapine, but that after another five weeks of treatment there was increased rCBF in this region (Lahti et al., 2009). Studies in healthy controls further support the existence of divergent effects dependent on antipsychotic type. In a repeated measures, placebo-controlled study of 20 healthy volunteers, aripiprazole led to immediate increases in rCBF in the temporal cortex, whilst haloperidol led to decreases in this region (Handley et al., 2013). These studies highlight the need to consider the treatment type and duration when interpreting results.

Whilst at baseline patients had lower perfusion in the temporal lobe compared with healthy controls, and at follow up there was increased perfusion in this region, changes in temporal perfusion were not detected by the longitudinal analysis. The only region of significantly increased perfusion in patients was seen in the left superior parietal lobe, which extended into the left frontal lobe. The parietal cortex is not often implicated in the effects of antipsychotics on perfusion, but altered frontal perfusion is reported across the literature. Some previous studies have reported increases in frontal regions

with antipsychotic treatment (Sabri et al., 1997; Novak et al., 2005). However, not all studies have replicated this, with some reporting decreased rCBF in parts of the frontal cortex (Warkentin et al., 1990; Livingston et al., 1998). These inconsistencies may be due to a number of methodological differences between studies, as well as sample heterogeneity within and between studies (Marco et al., 1997). However, our study provides a relatively homogeneous sample of antipsychotic-naïve FEP, within the early stages of their illness. Therefore, my results would support that there are increases in frontal perfusion, alongside parietal increases, following antipsychotic treatment at this early stage. Inconsistencies may also be due to oversimplification of the cortical regions within the frontal lobe (treating it as a homogeneous region without divisions). The frontal lobe is a large brain region, which can be divided into a number of smaller sections with distinct cytoarchitecture and function. It is therefore possible that there are both increases and decreases within the frontal lobe following antipsychotic treatment but occurring in different regions within this lobe.

Few, if any, studies have previously investigated the effects of antipsychotics on rCBF in patients with psychosis longitudinally using ASL. This technique is a relatively novel method of imaging perfusion, and has been used to show correlations between rCBF and regional brain activity measured by other techniques (Uludag et al., 2004). However, interpretation of perfusion data must bear in mind that mechanisms other than brain activation may play a role in alterations seen. The role of receptor-level factors, such as up- and down-regulation, have been discussed by some authors (Jenkins, 2012), whilst others have highlighted the need to consider global, systemic effects of drugs, such as direct effects on blood vessels (Viviani et al., 2013). The differences seen are therefore complicated to interpret and may not simply reflect functional or structural alterations, although it might be expected that there are relationships between these neurobiological changes. The direction of these relationships remains unclear, however. It is possible that structural changes precede

and lead to changes in perfusion, and vice versa. Multimodality longitudinal studies across illness progression may provide insight into these relationships.

My results suggest that patients already differ from healthy controls before they are treated, and that antipsychotic treatment alters rCBF. However, it seems probable from my analyses that differences in perfusion patterns in schizophrenia also depend upon response to treatment. It is possible that the effects of antipsychotic medication on the brain differ between those who respond well and those who respond poorly to medication. I therefore investigated these two groups of patients in my sample and discuss my results below in section 4.1.2.

4.1.2 Associations between clinical, behavioural, and neurobiological measures and treatment response

Whilst increasing evidence supports the effects of antipsychotics on the brain, it remains unclear whether the effects observed are associated with clinical improvement. A major focus of this project was to investigate the associations between the measures taken (clinical, behavioural, and neurobiological) and response to treatment. Whilst antipsychotic medications are the first treatment choice for psychosis and show group-level efficacy (Leucht et al., 2013), at an individual level response to treatment is variable (Barnes, 2011). Identifying the differences between patients who show a good response to treatment and those who show a poor response to treatment is key to understanding the mechanisms of treatment response. Furthermore, this may allow for prediction of response as outlined later in section 4.1.3. Biological factors may be particularly important, and elucidating the biological variation underlying treatment resistance and poor response may improve treatment for patients, reduce costs for services, and provide potential new treatment targets. In this project, I investigated treatment response in several ways, comparing responders and non-responders directly, as well as comparing each with healthy controls. One of the main implications of my findings is that in patients with psychosis, the neurobiological differences

between responders and non-responders are more marked than those between patients and controls. This heterogeneity in terms of response to treatment may reflect differences in the underlying neurobiology.

a) Clinical measures

Whilst there was a general improvement in psychotic symptomatology following treatment, at an individual level there were differences in response to treatment among patients. Seventeen patients (68%) showed a good response to treatment, meeting the Andreasen et al., (2005) criteria for remission. Eight patients (32%) did not meet these criteria and so were designated non-responders. These proportions are in line with previous estimates of response rates in psychosis (Barnes et al., 2011).

Interestingly, DUP was longer in those classified as non-responders at four weeks than in responders. Furthermore, a longer DUP was associated with a smaller mean percent change in total PANSS scores. This is consistent with findings in the literature (Emsley et al., 2008). In this study, the relationship was likely driven by changes in positive symptoms, as there was a negative correlation between DUP and mean percent change in positive symptoms but no relationship with any of the other subscales. However, at 12 weeks, treatment response was no longer related to DUP, suggesting that this factor may be related to initial response but not longer-term outcomes. The only other demographic factor associated with treatment response was employment, as being employed was associated with greater improvements in positive symptoms as assessed by mean percentage change. This may be related to severity of illness, particularly if baseline symptom scores were related to later response, as patients with more severe symptoms at baseline might be less able to work and may also be less likely to respond to treatment.

This suggestion was supported by my analysis of the relationships between PANSS scores and treatment response. Non-responders at both four and 12 weeks had higher total PANSS scores than responders at both baseline and after four weeks of

treatment. This suggests that the more severely ill were less likely to have a good initial response, as well as being less likely to respond in the longer term. In most cases, positive and general psychopathology symptom scores were related with outcome but negative symptom scores were not. As such, antipsychotic treatment response depends more on severity of positive and general psychopathology symptoms than on negative symptoms. Previous studies have shown better premorbid adjustment, less severe pre-treatment symptoms, and shorter DUP to be associated with a better response to antipsychotic treatment (Perkins et al., 2005). Furthermore, some previous results have shown that whilst more severe hallucinations and delusions at baseline are associated with poor treatment response, negative and depressive symptoms were not related to outcome (Robinson et al., 1999). Furthermore, I found that negative scores did not significantly change with treatment. Previously, antipsychotic treatment has been found to have a greater effect on positive symptoms than on negative or cognitive symptoms of the disorder (Gardner et al., 2005).

Remission status remained relatively stable, with most patients who were classified as a responder at four weeks remaining so at 12 weeks. Furthermore, when I compared responders and non-responders classified at 12 weeks on clinical measures of psychopathology at four weeks, I found that there were already significant differences in positive PANSS and CGI at this stage. Together, these results suggest that patients who were less severely ill at four weeks, remained so throughout and continued to be good responders at 12 weeks. This is consistent with previous studies that have suggested that an early good response to treatment predicts subsequent good response (Levine and Leucht, 2012; Giegling et al., 2012; Ruberg et al., 2011). However, data were available for fewer patients at 12 weeks than at four weeks. Therefore, it is uncertain whether those patients not included in the analysis at 12 weeks continued to respond in the same way to antipsychotic treatment in the longer term. There were no relationships between the other clinical measures and treatment response at either four or 12 weeks or with percent change scores. However, CGI

severity at four weeks did significantly differ between responders and non-responders at 12 weeks. This again suggests that illness severity after four weeks treatment may predict longer-term response to treatment. These results show that in line with previous research some demographic and clinical characteristics of our patients were related to their response to antipsychotic drugs.

b) Behavioural measures of salience attribution

Although when comparing salience attribution in the whole patient group versus that of healthy controls few differences were found, this may be because salience attribution abnormalities are related to response to treatment. I found several differences in salience attribution processing between patients who showed a good response to treatment and those who showed a poor response to treatment. I also observed more differences between patients and healthy controls when patients were separated according to response. These results suggest that salience attribution abnormalities may differ in patients showing differences in response to treatment, perhaps reflecting differences in underlying pathology of their illness. Therefore, dividing patients according to treatment response might provide a clearer view of disrupted salience attribution processes in psychosis.

Previous studies have suggested that patients with psychosis have lower levels of adaptive salience compared with healthy controls (Roiser et al. 2009) and some suggest that this may actually be related to antipsychotic treatment (Smieskova et al., 2015). Indeed, within the framework of the aberrant salience hypothesis, it has been suggested that psychosis is primarily a disorder of aberrant salience processing, in which importance (salience) is attributed to neutral stimuli (Kapur, 2003). However, Kapur also talks about the dampening of salience by antipsychotic treatment (Kapur, 2003). It might be that antipsychotic medications reduce aberrant salience, but also reduce adaptive salience, leading to “deficit-like states” in which patients exhibit negative symptoms including dysphoria, withdrawal and so on. My results suggest that

this may be more complicated than previously thought, with response to treatment playing a role in determining the patterns of salience attribution seen.

Comparing responders and non-responders, I found that there were lower levels of implicit adaptive salience at baseline in those showing a poor response to treatment at baseline. However, this was no longer observed at follow up. When compared separately with healthy controls, both responders and non-responders showed adaptive salience deficits. However, only non-responders showed such deficits in implicit adaptive salience. Responders appeared to be able to differentiate high- and low-probability cues implicitly, but were not able to explicitly learn and verbalise the relationships between cues and reward at either baseline or follow up. Conversely, non-responders showed neither the ability to implicitly differentiate high- and low-probability cues, or to explicitly learn or verbalise the relationships. However, non-responders did not show lower implicit adaptive salience scores than healthy controls at follow up. Given that patients did not experience a remission of symptoms, it seems unlikely that there was an improvement in adaptive salience as a result of the antipsychotic treatment. The group of non-responders was small and so it may be that the sample size was not large enough to detect any difference at follow up. There was still a large difference in implicit adaptive salience scores at this time point (non-responders mean: 1.98; healthy controls mean: 18.12), but the sample probably lacked power and so this difference was not significant.

Due to the small number of non-responders in my sample, I also investigated a continuous measure of treatment response (percent change in PANSS). I found that there was a positive correlation between baseline implicit adaptive salience scores and percent change in PANSS, such that those showing the greatest improvements had higher baseline adaptive salience scores. This supports the assertion that disrupted adaptive salience is related to poor response to treatment.

My results do not support the idea that adaptive salience is dampened as a result of treatment with antipsychotic medications, as the longitudinal analysis showed no changes in implicit adaptive salience scores of either responders or non-responders. Indeed, the only significant change in adaptive scores across treatment was an increase in explicit adaptive salience scores in non-responders. Previous studies have not taken into account response to treatment and so this may have affected their results. For example, Roiser and colleagues (2009) used treated individuals with FEP in their study and found lower adaptive salience in their patients compared with healthy controls. Potentially, the reduced salience is dominated by those in their patient group showing a poor response to treatment (which in my sample is associated with lower adaptive salience scores), whilst those showing a good response to treatment have less disturbed salience attribution and contribute little to the differences seen.

It was originally thought that psychosis would be characterised by the presence of aberrant salience, rather than by disruptions in adaptive salience (Kapur, 2003). Indeed, work in healthy populations with subclinical psychotic symptoms (Van Os et al., 2009) and individuals at ultra-high risk (UHR) of psychosis (Roiser et al., 2012) have shown a relationship between higher levels of aberrant salience and psychosis. However, this finding has not been replicated in FEP, where decreased adaptive salience but comparable levels of aberrant salience were reported in patients compared with healthy controls (Roiser et al., 2009). Possibly medication may play a modulatory role on both aberrant and adaptive salience, dampening both these processes. The FEP patients previously studied were mostly medicated, unlike those with subclinical symptoms or at UHR. This might mean that the aberrant salience of FEP patients had been decreased by the medication they were taking, and that simultaneously any adaptive salience they might previously have exhibited was also dampened, leading to a decrease in this measure compared with healthy controls. As my sample comprises antipsychotic-naïve or minimally treated patients followed over

treatment, it offers an excellent test of the effects of antipsychotic medications over time.

As discussed above, my results do not support an effect of antipsychotics on adaptive salience scores when analysed longitudinally. It is possible that this is due to the type of antipsychotic (amisulpride) used in this study. Amisulpride is an SGA and FGAs might differ in their effects on salience attribution. However, it is also possible that patterns of salience attribution depend not only on medication but also on whether or not individuals respond to that medication.

In my sample, although patients did not differ from healthy controls on measures of aberrant salience, there were differences when responders and non-responders were directly compared. Responders showed non-significantly higher levels of implicit aberrant salience at baseline compared with non-responders, which significantly decreased with treatment. Therefore at follow up, responders had significantly lower levels of implicit aberrant salience than non-responders. It is possible that different patients exhibit different patterns of salience attribution when they are untreated. Differences in salience disruptions underlying their illness may be associated with differences in individuals' response to treatment. As such, those who have increased levels of aberrant salience are more likely to respond well to treatment, whereas those who do not show this salience abnormality, but have decreased adaptive salience, are likely to respond less well to treatment. This latter may be consistent with the idea that non-responders and treatment-resistance is related to a predominance of negative symptoms (Stone et al., 2009).

Furthering this argument, it is possible to speculate that these differences are determined by differences in the neurotransmitter disturbances underlying the illness, with dopamine or glutamate differentially involved in producing symptoms. Increased aberrant salience is purported to result from disturbed dopamine signalling, for example increases in dopamine in the mesolimbic system (Kapur, 2003). Furthermore, current

antipsychotic medications primarily target dopamine, most acting as D2 antagonists that lower dopamine levels, leading to a reduction in psychotic symptoms (Stahl, 2013). As such, those who respond well to current treatments may have a primarily dopamine-based psychosis, which leads to increased aberrant salience. However, this increased dopamine (and associated aberrant salience) is dampened by the antipsychotic medication. As dopamine levels are reduced, aberrant salience levels would also be expected to lower, and if this is related to symptomatology, a good response to treatment would be seen. In contrast, those who show a poor response to treatment might have an alternative underlying pathology, in which dopamine plays less of a role but other neurotransmitter systems, such as glutamate, are involved. Hence, they would be less likely to respond to current treatments that target dopamine, as this would not be the primary dysfunction causing their symptoms. Studies in treatment-resistant schizophrenia have suggested that glutamate disruption might play a role in the aetiology of the illness of such individuals (Stone et al., 2007).

As a result, a vast area of research is now investigating the efficacy of medications that target glutamate to treat psychosis. A primarily glutamate-based pathophysiology might be related to lower levels of adaptive salience but not increases in aberrant salience, thus showing a greater predominance of negative symptoms such as withdrawal and flat affect. A psychosis associated with glutamate dysfunction would be less likely to respond to treatments that target dopamine and so such individuals might be less likely to show a good response to treatment. This theory would be supported by my results, showing lower levels of adaptive salience in non-responders. However, it is not possible to comment on the glutamate signalling in such individuals, or whether there are differences in glutamate function between responders and non-responders. These arguments are highly speculative and require much further research to support them. Positron emission tomographic (PET) studies are required to monitor dopamine levels in patients before and after treatment, alongside tasks such as the SAT, which can provide measures of salience attribution. In addition, whilst glutamatergic compounds

have shown some promise in early clinical trials (Stone, 2011; Noetzel et al., 2013), results remain few and inconsistent, and glutamatergic compounds are not yet available for regular use in the clinic to treat psychosis (Kahn and Sommer, 2015; Singh and Singh 2011). Therefore, further research regarding the pathophysiology underlying the illness of treatment non-responders and the reasons for their poor response to treatment is warranted.

Nonetheless, my results suggest that there are abnormalities in salience attribution processes of patients with psychosis compared with healthy controls. However, these abnormalities differ within patient groups, such that particular patterns of abnormality are related to response to treatment. Those who show a good response to treatment show greater aberrant salience, whilst those who show a poor response show disruptions in adaptive salience processes.

c) Neural activation during salience attribution measured using fMRI

Several previous studies have used different types of functional imaging to predict treatment response. For example, PET studies have indicated that a good treatment response is associated with greater striatal D2 receptor occupancy during treatment (Kapur et al., 2001; Nordstrom et al., 1993; Agid et al., 2007) and increased striatal dopamine synthesis capacity (Demjaha et al., 2012; Abi-Dargham et al., 2000). BOLD fMRI techniques have been used more rarely to investigate relationships between brain function and response to treatment. Studies using the n-back (a working memory task) have suggested increased PFC activity associated with improved symptoms following treatment with CBT (Kumari et al., 2009), as well as atypical antipsychotic medications (Honey et al., 1999; Meisenzahl et al., 2006). Unfortunately, these studies have not investigated differences between good and poor responders at baseline (before treatment commences) and so the results are of limited predictive use.

Only two studies have investigated the relationship between functional brain activation before treatment and later response to treatment (Van Veelan et al., 2011; Nejad et al.,

2013). Both these studies investigated working memory activation and found that particular patterns predicted later response to treatment. Van Veelan and colleagues (2011) found left dorsolateral PFC abnormalities in non-responders only, and that responders did not differ from healthy controls. Nejad and colleagues (2013) looked at functional connectivity, and found activation in a frontoparietal network that predicted improvements in negative symptoms. It is difficult to compare these studies to my own results as they are investigating a different aspect of brain function. No previous studies have investigated salience processing in relation to treatment response within a fMRI paradigm. As such, my results provide the first indications of whether measures of neural activation underlying salience processing are good potential biomarkers of treatment response in FEP.

Indeed, given the wide range of potential tasks, each tapping a different area of cognition, functional imaging provides a huge potential for predictive biomarkers. However, there is also a danger that too much variation in task choice prevents comparison between studies and makes it difficult to generalise results. It is necessary to choose appropriate functional tasks based on theory and a priori hypotheses. The use of standardised, commonly used, validated tasks for particular functions is also desirable. A good example of this is the n-back task, which is often used to probe working memory processes. There is no standard task for the investigation of salience attribution. Whilst various tasks are commonly used to provide measures of various aspects of reward processing, none offers specific measures of salience attribution, both at implicit and explicit levels. The SAT might therefore be good candidate for future studies investigating salience attribution in relation to treatment effects and treatment response.

My results showed that whilst there were few differences between healthy controls and the entire patient group, several differences became apparent when patients were divided according to response. This may suggest that patients showing a good response have different underlying pathophysiology to those showing a poor response,

as discussed above. This was first illustrated by comparing four-week responders and non-responders directly. At baseline, four-week responders had higher activation in the insula and cerebellum than non-responders during adaptive salience processing. Four-week responders also had activation in frontal regions during adaptive salience processing that was not seen in non-responders. At follow up, responders had higher activation in the midbrain, again associated with adaptive salience.

The insula is a region of cortex at the base of the lateral sulcus, and plays a role in various aspects of emotions, perception, and cognition (Gasquoine, 2014). Furthermore, the insula, along with the anterior cingulate cortex, is thought to be part of a salience network, which enables switching between the default mode network at rest and task-related states of brain activation (Palaniyappan and Liddle, 2012). Structural and functional abnormalities in the insula have been reported in a range of psychiatric disorders, including autism, eating disorders, anxiety, and schizophrenia (Gasquoine 2014). Meta-analyses support the existence of bilateral volume reductions in the insula in schizophrenia, unrelated to illness stage or sex (Shepherd et al., 2012). Furthermore, decreased gyrification in the insula may be related to poor treatment response (Palaniyappan et al., 2013). In a functional study, reduced prediction error signals in the insula during instrumental reward learning were reported, which correlated with positive symptom severity (Gradin et al., 2011). This is consistent with my results in which four-week non-responders, who had more severe positive symptoms than responders even at baseline, had reduced insula activation during salience attribution. Activation in this region could therefore provide a potential biomarker for treatment response.

I also compared responders and non-responders each in turn with healthy controls. Consistent with Van Veelan and colleagues (2011), I did not find any differences between responders and healthy controls at baseline. However, non-responders did differ from healthy controls, with decreased activation in the cerebellum. Whilst the cerebellum has traditionally been associated with motor control and coordination, more

recent studies have implicated this structure in emotion regulation and cognition (Shakiba, 2014). What's more, cerebellar abnormalities have been implicated in several psychiatric disorders, such as bipolar disorder, depression, and anxiety disorders, in addition to schizophrenia (Philips et al., 2015). It is interesting that whilst four-week responders in my study did not show any activation changes with treatment, bilateral increases in the cerebellum associated with adaptive salience processing were seen in non-responders. It is not clear how cerebellar activation relates to symptoms, as non-responders remained symptomatic despite this increase in activation. Furthermore, at follow up they no longer differed from healthy controls in this region.

Different regions were associated with response to treatment when longer-term response was considered. At baseline, the comparisons of 12-week responders and non-responders identified differences in the superior temporal and middle occipital lobes. At follow up, there were no longer any differences between these two groups. Similarly to four-week responders, those designated as responders at 12 weeks did not show any differences from healthy controls at either baseline or follow up. Long-term non-response appears to be associated with reduced activation during adaptive salience in the cerebellum before treatment commences. After four weeks of treatment, 12-week non-responders had lower activation in the frontal lobe and posterior cingulate associated with aberrant salience. These results suggest that altered activation during adaptive salience processing is associated with both short- and longer-term poor response to treatment. However, those patients showing a good response to treatment, both in the short- and longer-term, did not differ significantly from healthy controls. These differences are apparent before treatment initiation and so may be potential predictive biomarkers for treatment response.

It is interesting that there were mainly differences during adaptive salience processing, and fewer during aberrant attribution of salience. Moreover, there was a clear link between adaptive salience abnormalities and treatment response, whether this was defined by the Andreasen criteria or by percentage PANSS change. This is consistent

with recent currently unpublished research investigating ultra high-risk (UHR) participants (Schmidt et al., in prep), where normalisation of adaptive salience processing was associated with improvement of delusion-like symptoms. Whilst good treatment response is associated with greater abnormalities in dopamine signalling, they are here exhibiting less marked abnormalities in adaptive salience processes. This may suggest that rather than increased or aberrant dopamine signalling, it is a lack of dopamine that underlies adaptive salience abnormalities. This would be consistent with my finding that there is underactivation in the midbrain of non-responders after four weeks of treatment, potentially suggesting that antipsychotic treatment had failed to normalise dopamine function in this region.

Adaptive salience abnormalities may therefore be more significant in the development of psychosis, particularly in those who are unlikely to respond to currently available treatments. This is consistent with the argument outlined above, that non-response is related to decreased adaptive salience, which may relate to differences in underlying neurotransmitter disturbances. Whilst increased aberrant salience may result from disturbed dopamine signalling, for example increases in dopamine in the mesolimbic system (Kapur, 2003), disturbed adaptive salience attribution may relate to a primary glutamate dysfunction, which would not respond well to current treatments targeting dopamine. As stated above, such speculation requires much further research to establish whether this is the case.

It is also worth bearing in mind that the sample size was low with both four- and 12-week response. In particular, there were very few non-responders at either of these time points. Therefore, these results are preliminary and should be interpreted with caution. Nonetheless, my results suggest that there are differences between responders and non-responders at the level of both behaviour and neural activation during salience attribution processing, particularly adaptive salience.

d) Resting CBF measured using cASL

Few studies have previously investigated the association between rCBF and treatment response longitudinally in psychosis. To my knowledge, just four have done so (Rodriguez et al., 1996/1997; Lahti et al., 2009; Ertugrul et al., 2009) and none of these used ASL. Furthermore, their patient samples have often been previously exposed to antipsychotics making it difficult to discern whether the effects reported were the result of treatment withdrawal, chronic antipsychotic use or the study drug. Nevertheless, there were some similarities between these studies and my results. Similar to previous work, I found that the precise pattern of effects of antipsychotic treatment (in this case with amisulpride) on brain perfusion depends on treatment response. Furthermore, patterns of perfusion observed at baseline differed between those who later showed a good response and those who showed a poor response to treatment. As these differences were present before treatment had begun, they may potentially provide predictive biomarkers of treatment response (see discussion of support vector machine learning below).

At baseline, antipsychotic-naïve/minimally treated patients who later responded well to four weeks of amisulpride had higher rCBF in regions of the cerebellum and in the bilateral thalamus than those who went on to show a poor response to treatment. This is consistent with the work of Rodriguez and colleagues (1996/1997) who found greater thalamic perfusion, as well as greater perfusion in the basal ganglia and right PFC at baseline associated with a good response to clozapine. In addition, thalamic rCBF ratios (relative to homolateral cerebellar rCBF) predicted response correctly in 78.9% of cases. However, patients in this study were treated with FGA at baseline, to which they had not responded. It is possible that increases in thalamic and basal ganglia perfusion resulted from the FGA. Indeed, Lahti and colleagues (2009) reported increases in a region of the basal ganglia, the ventral striatum, following treatment with haloperidol or olanzapine.

I also found that higher baseline rCBF in the thalamus of my patients was significantly correlated with lower PANSS scores at four-week follow up. Elsewhere, baseline thalamic rCBF has been shown to predict percent change in PANSS after eight weeks of clozapine treatment (Ertugrul et al., 2009). However, it is worth highlighting that percent change scores do not necessarily indicate clinically relevant improvement. As such, whilst higher rCBF in this structure might predict bigger changes, it is not necessarily associated with remission, and patients exhibiting this trait may therefore still be ill following treatment. Nonetheless, the presence of differences associated with later clinical improvement evident before treatment has started suggests that rCBF may have some value in predicting response to antipsychotic treatment.

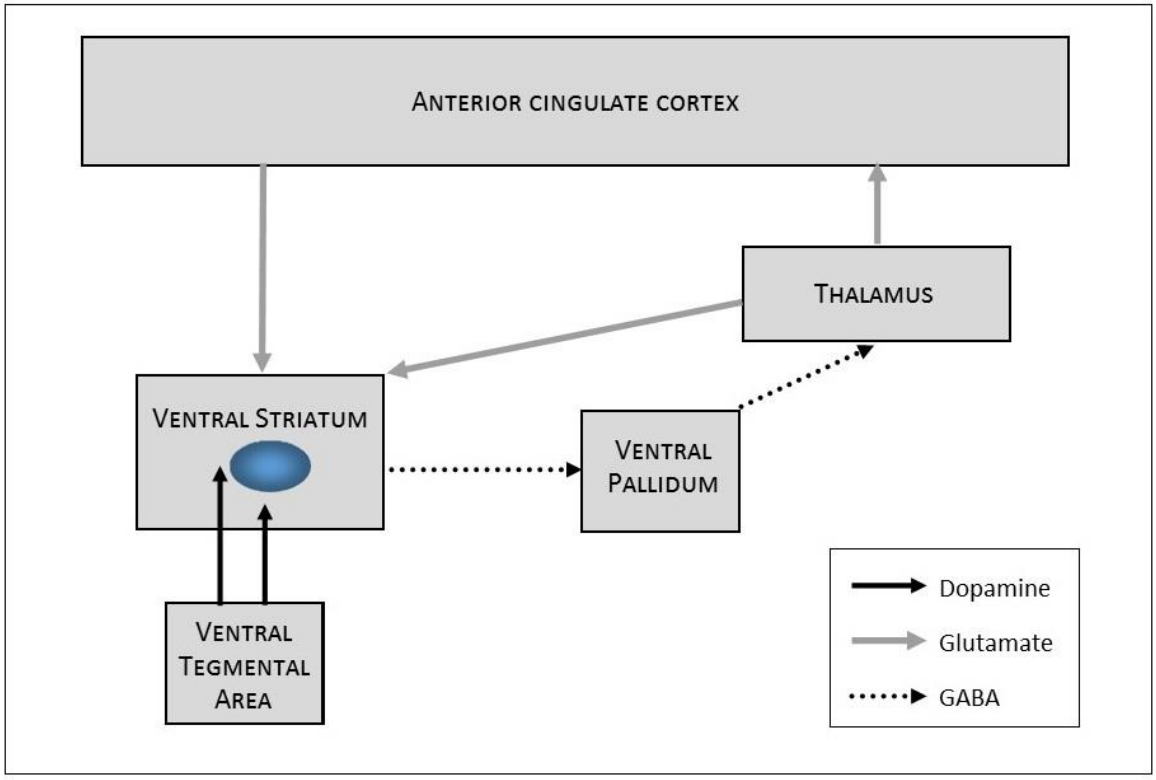

Figure 45: *Simplified diagram showing the connectivity between the thalamus and cortical and subcortical regions (adapted from Lahti et al., 2009).*

The ventral striatum is an area rich in dopamine (DA) D2-receptors, and is likely a key site of initial antipsychotic action. Receiving DA (from the ventral tegmentum) and glutamate (GLU; from the anterior cingulate) inputs, the ventral striatum projects GABA efferents to the ventral pallidum, which in turn projects to the thalamus. The thalamus has glutamatergic projections to the PFC. The action of antipsychotics in responders and non-responders appears to have different effects. In responders, it is possible that previously elevated DA is opposed through D2 blockade, which restores GLU transmission. In non-responders, this does not occur and GLU transmission remains impaired.

The thalamus appears to be a key structure in schizophrenia, particularly as part of fronto-strital-thalamic networks (Figure 45). It is a highly interconnected structure, with projections to and from cortical regions and the brainstem, and it has been posited as a "gating" or "filtering" region, playing a major role in human cognition (Andreasen, 1997). Furthermore, models of schizophrenia have proposed the thalamus to be a crucial brain region that could underlie a broad information processing deficit underlying the pathophysiology of schizophrenia (Carlsson and Carlsson, 1990). Aside from the studies investigating perfusion described above, abnormalities in thalamic structure and function have been reported elsewhere in the literature, including decreased neuronal density and volume (Pakkenberg, 1992; Andreasen et al., 1990; Flaum et al., 1990), decreased white-matter projections to the PFC (Andreasen et al., 1994), and abnormal activation during active hallucinations (Sibersweig et al., 1995).

It has been proposed that the action of antipsychotics on the connections to the thalamus may differ in responders and non-responders (Lahti et al., 2009). The ventral striatum is a key site of antipsychotic action, rich in dopamine (DA) D2 receptors. PET studies have shown increased striatal DA release in drug-free patients (Laruelle et al., 1996), which is predictive of treatment response (Abi-Dargham et al., 2000). It is possible that excessive DA signalling in the ventral striatum leads to increased GABAergic signalling via the ventral pallidum, which, in turn, reduces thalamic glutamatergic transmission to the PFC. Antipsychotics acting at the ventral striatum site would block excessive DA signalling, releasing the inhibitory GABAergic effects on the thalamus, and thus restoring glutamate signalling to the PFC and other thalamic projection sites. However, this process may only occur in responders, but not in non-responders, where glutamatergic signalling remains impaired (Lahti et al., 2009). Precisely why non-responders would not show the same effect remains a matter of speculation. It is possible that the pathophysiology of their symptoms is not primarily due to excessive striatal DA signalling, and so drugs targeting this region have little effect. As outlined in section 4.1.2. b) above, it has been proposed that in individuals

with schizophrenia who show a poor response to current treatments the pathophysiology underlying the illness could be influenced by other neurotransmitter systems, such as glutamate (Stone et al., 2007). As previously suggested, drugs targeting glutamatergic dysfunctions may therefore be more effective in treating those who respond poorly to drugs targeting primarily the dopamine system.

Although in my sample I observed alterations in the thalamus associated with treatment response, there was no effect seen in the ventral striatum or other regions connected with the thalamus. However, the relationships between imaging parameters is complex and it is possible that PET in the same subjects would have revealed increased dopamine release in these regions. Multimodal studies in the same subjects would be informative in this regard, and could aid the investigation of relationships between the alterations seen in different measures, for example how changes in structure or metabolism relate to altered perfusion.

At follow up, there were no longer any differences between responders and non-responders. This may suggest that as in the studies by Rodriguez and colleagues (1997a/b) there is a decrease in thalamic perfusion following treatment. However, in their study participants were treated at baseline with FGA and then switched to clozapine. It is therefore possible that the FGA treatment was associated with increased thalamic perfusion, and that this increase was greater than that associated with clozapine. As such, following switching there appeared to be a relative decrease in perfusion in this region. This highlights the importance of treatment status at baseline. In antipsychotic-naïve individuals, one does not need to consider the complicating influence of current treatment on the brain measure of interest.

Few studies have investigated the relationships between perfusion and antipsychotic treatment response, and often the results obtained are conflicting. However, it may be unwise to try to pool results from studies looking at the effects of antipsychotics because there are likely to be differences in the effects of different types of

antipsychotics used. Particularly, FGA and SGA tend to be associated with different effects (Goozée et al., 2014). Even within the class of SGA, it is possible that there are different effects that reflect the precise mechanisms of action of the specific drug studied. Therefore, comparative studies of more than one antipsychotic medication administered to the same participant are necessary and may shed light on the differences in effects between drugs. This is likely to be a pertinent issue if personalised medicine is to develop beyond the prediction of benefit from broad categories of drugs. However, given the number of drugs available, to begin by comparing broader classes (e.g., FGA and SGA) may be a justifiable approach. Further understanding of the mechanisms of action of different antipsychotic medications may allow the development of different classification systems that provide some predictive value in terms of response to treatment for individual patients.

Supporting the assertion that studies are needed that compare different types of drugs, in a study of patients with schizophrenia treated for six weeks with either olanzapine or haloperidol, there were common regions of effects but also regions in which the effects of the two drugs differed (Lahti et al., 2009). Both drugs acted to increase rCBF in cortico-subcortical and limbic networks. However, in patients treated with haloperidol, good response was associated with greater activation in the left thalamus and lower activation in the left hippocampus at follow up. In contrast, in patients treated with olanzapine, good response was associated with greater activation in the cerebellum and lower activation in cortical regions (sensorimotor, middle and medial frontal, superior parietal, and anterior cingulate cortex) at follow up.

In addition to cross-sectional analyses, I also investigated the effects of amisulpride longitudinally in responders and non-responders. This revealed differences dependent on response to treatment. When responders and non-responders were assessed separately, responders were shown to have an increase in rCBF in the precentral gyrus, whilst non-responders did not show any changes. However, there was an overall decrease in global rCBF in non-responders that was not seen in responders. Increased

parietal rCBF was also seen in 12-week responders and non-responders, although the precise region differed slightly. These results suggest that there are longitudinal changes with antipsychotic treatment, which differ depending on whether patients later showed good or poor response to treatment. Furthermore, it suggests that there may be fewer effects of antipsychotic medication on patterns of regional brain perfusion in non-responders, who also show fewer changes in symptomatology. The global decrease in rCBF observed in non-responders may reflect a non-specific, diffuse effect of the drug that does not lead to improved symptomatology. Of course, as my group of non-responders was small, it is possible that the sample lacked power to detect any regional changes in rCBF.

As discussed above, interpreting perfusion is complex as a number of biological mechanisms may play a role. There are several mechanisms by which antipsychotics could lead to altered perfusion. It is supposed that perfusion reflects microcirculation and glucose consumption, and integrative synaptic processes (mostly postsynaptic) rather than spike rates of efferent cells (Lauritzen, 2001). However, this suggests that perfusion could reflect any number of events occurring at a synapse, including neurotransmitter interactions with receptors, production of second messengers, reuptake, and recovery of electrochemical gradients. Some authors have suggested a role for receptor-level factors, such as up- and down-regulation (Jenkins, 2012), which could provide a link between the dopaminergic changes seen with antipsychotic treatment and changes in blood perfusion to serve the altered metabolic associated with these changes. Others have highlighted global, systemic effects of drugs, such as direct effects on blood vessels (Viviani et al., 2013). However, my results suggest regional effects in addition to global effects, which are not adequately accounted for by global, systemic antipsychotic effects. Perfusion changes likely reflect functional or structural alterations also seen with antipsychotic treatment, and the changes in metabolic demand associated with these. Neural activation is coupled with blood oxygen use, and so changes in activation will likely be reflected in perfusion changes

(Theberge, 2008), although whether this relationship is direct is unclear. The direction of these relationships also remains unclear. It is possible that structural changes precede and lead to changes in perfusion, and vice versa. Multimodality longitudinal studies in humans across illness progression may provide insight into these relationships, alongside animal studies to determine the molecular and cellular processes underlying changes in blood flow.

Longitudinal analyses can show the dynamic changes associated with good or poor response, and may therefore aid the elucidation of mechanisms of response or new treatment targets for those showing a poor response. However, when considering prediction of response in a clinical setting, studying baseline differences can be more useful. Personalised medicine would benefit most from biomarkers that predict later treatment response but are present before treatment begins, allowing clinicians to assess the pre-treatment neurobiology of patients and pick a treatment that is likely to be successful on this basis. For this, support vector machine learning and other types of machine learning are promising to be useful tools (see below).

4.2 Limitations of the research

My sample was recruited from mainly outpatient services, during the first two years of illness. Furthermore, I could not recruit patients who were treated or admitted on an involuntary basis (under a Section of the Mental Health Act). These factors mean that the sample of patients I recruited were unlikely to be severely ill, as they were being treated in the community (all except one patient) and were well enough to consent to and take part in the study. This may limit the generalizability of the results. It has been reported that more than 70% of patients with a FEP are admitted to hospital (Byrne, 2007) and for many their first contact with services is via an admission often through accident and emergency departments (Payne et al., 2006). Furthermore, more severely ill patients may have more problems with adherence to treatment, which would affect the perceived efficacy of a treatment. Our patients were mostly quite willing to take antipsychotic medications, and were more closely supervised (by the research team in addition to the clinical team) than they would otherwise have been. Therefore, these results may not be applicable to more severely ill inpatients who would be less adherent to medication.

The less severely ill sample we recruited may also explain the relatively small number of non-responders (although we were close to the 40% reported by Barnes et al., 2011), as severity of illness may be related to later treatment response. Indeed, in our own sample, we found that baseline severity of illness (PANSS, CGI, and PSP) was related to later response to treatment, with non-responders being more severely ill at baseline than responders. However, having a small number of non-responders reduces the power of the statistical analyses carried out. I have attempted to overcome this by using a continuous measure of treatment response alongside a categorical definition, to provide further support for any relationships between the characteristics and clinical variables in patients and treatment response.

A further consideration in the interpretation of my results regards the length of time for which patients were treated. We assessed treatment response at four weeks. Most

patients are treated for much longer with antipsychotic medications. In some cases, a patient may take longer than this to show a response to treatment. However, I also used the PPHS to assess 12-week treatment response in order to gain an idea of how longer term outcome might be affected by the variables studied. However, it is possible that between these two time points antipsychotic medication was changed as part of the study protocol or by the responsible clinician. Furthermore, 12-week follow up was not available for a number of patients, limiting the sample size at this stage. However, previous studies have shown that antipsychotic medications have effects on the brain early in treatment, and many studies support that early response to treatment is strongly predictive of later response (see discussion above).

Indeed, sample size may be a limitation for the functional imaging results presented in this thesis. Nonetheless, the power calculations on page 113 of the Methods suggest that a sample size of 16 participants would be required to have 80% power at p=0.05 to detect an effect size of 0.9, between response groups at baseline on the SAT. This is less than the effect reported by Roiser et al. (2009) comparing patients with and without positive psychotic symptoms (d=1.6). This suggests that my sample was sufficient. Nonetheless, future studies should aim to recruit larger samples, which could be aided by large multicentre trials.

A major strength of this study was its focus on recruiting a more homogeneous patient group than has previously been studied. Ideally, patients who are entirely antipsychotic-naïve would be recruited and scanned prior to any medication being prescribed. However, in reality this is incredibly difficult to achieve, given pathways to care and our ability to identify patients before treatment, as well as ethically dubious if we are to arrange study practicalities without delaying much-needed treatment. For this reason, most of our patients were in fact minimally treated rather than completely naïve. However, even short term and single doses of antipsychotic drugs have been shown to affect the brain (Handley et al., 2014). We must therefore be cautious in interpreting the findings from baseline brain scans, as they may already reflect changes

related to the treatment patients received prior to this. However, the duration of previous treatment was limited to a maximum of two weeks, and the mean period of treatment prior to the first scan was just 8.76 days (S.D. 7.74). It would be more of a concern if there were differences between responders and non-responders regarding treatment prior to the first scan, as this might be responsible for differences seen between the two groups. However, when this was directly compared, there was no significant difference ($t(23)=-0.21$, $p=0.83$).

The longitudinal design of this study is a strength as it enables investigation of changes over treatment within the same individuals. However, longitudinal designs, with individual patients being followed up over time, invite a risk of drop out. If patients do drop out of the study it is worth considering whether there were any differences between patients completing follow up and those who dropped out. In this study, we had follow up clinical scores for all patients, and cASL imaging for all patients. Only two patients completed a baseline fMRI scan and did not complete the follow up. As this is a relatively small number of patients, it is unlikely that this would have affected my results.

In this study, the use of a single antipsychotic drug ensured that the effects seen could be interpreted more easily within the context of the mechanisms of action of this particular medication. However, it limits the generalizability of the results somewhat. Patients in real life are treated with a range of antipsychotic medications and these results do not allow us to directly apply the predictive biomarkers found to these other drugs. Furthermore, the results cannot aid the clinical choice between antipsychotic medications by informing us of which patients would benefit from which specific drug. Future studies comparing different classes and different specific antipsychotic medications are necessary. However, using a single antipsychotic with a relatively pure mechanism of action at D2 receptors is a strength at this early stage.

Finally, this study justifiably focuses on the early stages of psychotic illness. Many current patients who have been ill for a long time and previously treated, may also have

inadequate management of symptoms and might benefit from medication optimisation through predictive biomarkers to avoid the need for more lengthy trials of alternative medications. However, the results in this study are only relevant to patients who are first beginning treatment. Whilst it is clear we wish to target patients early on and prevent chronic illness, the many individuals who are already ill with poorly managed treatments may not benefit from this kind of research. Nonetheless, the ultimate aim of research into predictive biomarkers is that patients will receive appropriate and effective medication early in their illness, preventing the progression of the disease. Furthermore, the importance of investigating antipsychotic effects in patients with little prior exposure to these medications is clear, when attempting to disentangle disease and medication effects.

4.3 Implications for future research

4.3.1 Personalised medicine

The ultimate aim of research such as that pursued in this thesis is to develop a system of personalised treatment for patients with psychosis. Personalised medicine uses genetic, proteomic, and neuroimaging biomarkers to inform the diagnosis, treatment, and management of illness in individual patients. This approach assumes that individuals have unique biological characteristics that influence their diagnosis and response to therapies (Ozomaro et al., 2013). Here, I have been particularly concerned with the prediction of response to treatment in psychosis. Personalised medicine is an approach that has been adopted successfully in various areas of physical health (e.g. oncology), and is increasingly a focus in psychiatric illnesses.

Personalised medicine would hold a number of benefits for both individuals and society. Some patients with psychosis do not respond to the first antipsychotic prescribed and we cannot currently predict who will respond and who will not (Barnes et al., 2011). As such, patients may undergo a series of treatment 'trials' until they find an antipsychotic that works for them. This can be associated with a degree of suffering on the part of the patient, as well as associated detrimental effects on their social and occupational functioning. In addition, there is a societal cost associated with poorly treated illness, including the extra time and money required to treat residual symptoms and associated morbidity, adverse drug reactions and side effects (Piquette-Miller and Grant, 2007). Therefore, discovering biomarkers that are predictive of response to treatment would allow drug treatments to be tailored to the pathophysiology underlying a particular patient's illness.

Such biomarkers could be integrated into routine clinical practice, if tools were developed that could detect them at an early stage. Thus, a patient diagnosed with a first episode psychosis might receive an MRI scan or a blood test as part of their initial assessment. The results of such an investigation could then be used to determine

which treatment the patient is likely to benefit from, prior to initiation of treatment. This would avoid the need for lengthy treatment trials, in which various medications are trialled unsuccessfully before one is found to be effective. I discuss the potential for clinical application of such biomarkers below (page 293).

In this line of research, it is important to not only consider the factors that determine a good response to treatment, but also those that are associated with non-response. Many studies focus on the clinical or biological variables that predict a favourable treatment outcome. It is important that we do not neglect the neurobiological signatures of a poor response. The former will allow us to practice personalised medicine, the latter will identify those who may not respond to any current treatments. Therefore, understanding the mechanisms of their lack of response may provide new treatment targets, to allow new drugs to be developed that can provide benefit for those who currently show a poor response to all available antipsychotic medications. Research that pursues alternative treatments for those who do not respond to current dopaminergic drugs is already underway, with the most obvious example being glutamatergic compounds. The development of effective alternative treatments will be aided by identification of neurobiological alterations that are found in non-responders and can be targeted by new compounds.

Of course, this study only considered a single antipsychotic medication, amisulpride. For predictive tools to be useful clinically, future research will need to investigate a range of different treatments. It is possible the factors predicting a good response to different antipsychotic medications differ, depending on the precise mechanisms of action of that drug. Indeed, as we have seen results from several studies in which more than one antipsychotic has been investigated suggest that there are differential effects of different medications. Whilst a broad division between FGA and SGA can be drawn, it is possible that future research will further differentiate between the actions of drugs from within these classes to add extra precision to the selection of a medication for an individual's treatment plan.

Despite the promises and optimism of research in personalised medicine in psychiatry, some have criticised the relative paucity of primary research studies compared with reviews and commentaries (Holmes et al., 2009). However, as the field progresses this will hopefully change. Others have suggested that personalised psychiatric practice will not determine which of a range of drugs a patient should be prescribed but rather will exclude those unlikely to have an effect in a small number of patients (De Leon 2009). However, it is possible that integrative approaches, using information from neuroimaging, as well as genetics and proteomics, may provide more accurate predictions (Costa e Silva, 2013). Furthermore, network and multivariate approaches are promising new avenues that better reflect the nature of the pathophysiology underlying complex psychiatric disorders and will aid our understanding of the biological mechanisms of aetiology and treatment response.

4.3.2 Clinical application

Currently, personalised approaches to treatment in psychiatry are not at the stage where they could be implemented in the clinic. This field is still a burgeoning field, but there is promise that the search for useful predictive biomarkers of response to treatment will be fruitful. Although much further work is required to identify reliable and accurate predictive biomarkers, it is necessary to consider some of the implications of this line of research in the clinic, and some of the barriers there may be in applying the tools clinically.

Several biomarkers have been investigated as potential predictive tools for refining treatment of individual patients. The neuroimaging techniques proposed, such as those used in the current project, hold a number of advantages as potential predictive tools. Firstly, they are safe to use and entirely non-invasive. Aside from some contraindications (such as claustrophobia and metal implants in the body), most patients will be able to undergo an MRI scan. Secondly, these scans can be quick and are not taxing for the patient, particularly if resting state measures are used. Of course,

the patient's illness state may be important. It needs to be considered at what stage of illness it is optimal to scan a patient to inform treatment. Clearly, it would be desirable to scan a patient as early as possible to start treatment as soon as possible, in line with early intervention approaches to the treatment of psychosis. However, this would have to be balanced with the presence of acute psychotic symptoms that may make a scan impractical or particularly uncomfortable for the patient.

Of course, the uptake of new practice and new tools in the clinic is determined by a number of factors beyond simply the effectiveness and availability of the new technology. MacQueen (2010) has outlined some of the potential barriers to uptake, including policy issues. For example, there must be consideration of how to deal with the large amounts of personal and potentially sensitive information created by a personalised medicine approach. Furthermore, detailed cost-benefit analyses are yet to be conducted. MRI scans can be costly and psychiatric illnesses are relatively common, which may mean a high demand for such assessments (MacQueen, 2010). Nonetheless, it is possible that compared with the cost of poorly managed psychiatric illness, the outlay for such assessments may prove more cost-effective in the long term. Detailed cost-benefit analyses are required to answer such questions.

A hugely influential factor in the uptake of such technologies for the diagnosis, treatment, and management of psychiatric disorders will be psychiatrists themselves. Indeed, it is possible that a cultural change will be required before such tools could be successfully integrated into clinical practice. Psychiatrists are generally trained to take a holistic view of their patients, and so may reject the impersonal nature of a scan that does not consider other psychosocial factors. Indeed, for many psychiatrists, the term 'personalised medicine' refers to the consideration of other psychosocial factors into the treatment of an individual. Therefore, introduction of the technology would require some education and training for clinicians, and it would need to be incorporated into the holistic approach that is embedded within current psychiatric practice. Importantly, some psychiatrists may feel as though new technology, which appears to make

decisions on their behalf, threatens the importance of their clinical judgement, gained through long-term knowledge of a patient and the insight gained into each individual's unique experience of an illness gained from more traditional psychiatric assessment. Indeed, psychiatrists do not currently use laboratory tests in their practice, but as suggested by MacQueen (2010) the curriculum for specialty training could be developed to reflect recent advances in biological psychiatry and to try to oppose the development of 'neurophobia' amongst newly qualified psychiatrists (Bullmore et al., 2009). Such changes may facilitate the incorporation of scanning for predictive biomarkers into regular clinical practice.

4.3.3 Future research directions

My results suggest that patients with psychosis differ in underlying neurophysiological processes, as well as relevant behavioural measures, based on whether they show a good or poor response to treatment. There are also differential effects of antipsychotics on the brains of responders and non-responders. Personalised medicine hopes to discover such associations, and find biological markers that can predict clinical improvement before treatment, such that drugs can be targeted to particular individuals based on the pathophysiology of their disorder.

It is particularly important to confirm whether there are differences between these patients before treatment commences. I found several differences at baseline between patients who later showed a good response and those who later showed a poor response. That these differences are present before treatment is important if neurobiological measures are to be used to predict treatment response. Whilst it is interesting to note the differences in prospective dynamic changes in neurobiological measures during treatment depending on response to treatment, these differences could not be used to guide treatment choice in a personalised manner that avoids trial and error, as discussed elsewhere in this thesis.

A new technique that holds particular promise is support vector machine learning (SVM), a pattern recognition method that models brain activity as activation within distributed networks and can be used to predict outcomes at an individual level (Mourao-Miranda et al., 2012). Very few studies have used this technique to predict treatment response, although it has shown promise in predicting transition to psychosis (Koutsouleris et al., 2009; 2012) or longer-term prognosis (Mourao-Miranda et al., 2012). Further work on the data used in this thesis will investigate the potential for SVM to be applied to measures of resting perfusion and functional activation during the SAT to predict outcome to treatment. Patient recruitment in the OPTiMiSE study continues until April 2016, which will increase the sample size. This would be an advantage as the sample used in this thesis is relatively small for pattern recognition procedures, particularly those categorised as non-responders.

Further research building on the results of this thesis should also consider the integration of multiple imaging modalities to further understand the neurophysiology underlying psychotic symptoms and response to treatment. In particular, PET imaging alongside perfusion imaging could relate dopaminergic alterations reported in patients to brain blood flow.

My results provide promise that neuroimaging markers could be used for the prediction of treatment response. They would offer safe, non-invasive tools that enable clinicians to improve management of psychosis with pharmacological treatments, by ensuring a more personalised and targeted approach is used in medication choice.

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APPENDIX A

Goozee, R, Handley, R, Kempton, MJ, Dazzan, P (2014) A systematic review and meta-analysis of the effects of antipsychotic medications on regional cerebral blood flow (rCBF) in schizophrenia: Association with response to treatment. *Neuroscience and Biobehavioural Reviews* 43: 118-136.

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Review

A systematic review and meta-analysis of the effects of antipsychotic medications on regional cerebral blood flow (rCBF) in schizophrenia: Association with response to treatment

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ABSTRACT

Evaluating the short- and long-term effects of antipsychotics on brain physiology is a key factor in advancing our understanding of neurophysiological changes in psychosis and improving prediction of treatment response. Understanding the nature of such changes is crucial to the interpretation of neuroimaging findings in patients with schizophrenia and psychoses in general. This review has systematically appraised existing evidence on resting cerebral blood flow (rCBF) in schizophrenia, before and after antipsychotic treatment, relating the findings to symptom severity. The review shows that antipsychotics exert regional effects on rCBF, particularly in frontal and basal ganglia regions, and that different antipsychotic generations have differential effects on rCBF. These findings are supported by an exploratory meta-analysis of a subset of studies. The review also highlights the relative lack of studies that use a priori definitions of treatment response, which is an important step in identifying testable hypotheses and ensuring clinical relevance of remission criteria. Finally, the review highlights important considerations for future psychopharmacological studies investigating the potential for rCBF to predict symptomatic improvement, which could inform the management of treatment in schizophrenia.

Contents

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1. Introduction

Although our understanding of the pharmacodynamic effects of different antipsychotics has advanced, the precise nature of their short and long-term effects on brain physiology remains unclear. Furthermore, it remains to be established whether physiological effects are specifically associated with clinical improvement. Understanding the nature of such effects is crucial to the interpretation of neuroimaging findings in patients with schizophrenia and psychoses in general.

Growing evidence suggests that some of the brain structural and functional changes observed in these disorders are partly related to antipsychotic treatment (Navari and Dazzan, 2009; Ho et al., 2011; Davis et al., 2005; Vita and De Peri, 2007). This evidence also suggests that different antipsychotics may be associated with specific alterations (Vita and De Peri, 2007), with first generation antipsychotics (FGA) particularly associated with increased basal ganglia (BG) and decreased frontal and temporal cortical volumes, and second generation antipsychotics (SGA) less so (Lieberman et al., 1987; Ho et al., 2011).

Among neuroimaging markers, altered resting cerebral blood flow (rCBF) is a measure of basal brain activity that has been related to both antipsychotic use and symptom amelioration (Pinkham et al., 2011). Most importantly, changes in rCBF patterns following antipsychotic administration have been reported in the same brain regions reported as altered in psychosis (Miller et al., 2001; Lahti et al., 2003). Moreover, these changes seem to occur within a few hours of single-dose administration, possibly in a generation-specific manner (Handley et al., 2012), hence demonstrating sensitivity of rCBF to early antipsychotic action.

Additionally, rCBF is closely correlated with neuronal metabolic measures (Raichle et al., 1976) and modern perfusion techniques, such as arterial spin labelling (ASL), show that rCBF correlates with regional brain activity measured using other techniques (Uludag et al., 2004), thus potentially representing a good physiological measure of antipsychotic effect. However, it should be borne in mind that changes in rCBF may not have the same origin as brain activation, as several other mechanisms may play a role in altered perfusion. For example, molecular mechanisms at the receptor level, including receptor distribution, up-regulation and down-regulation of receptors will all play a role in determining regional perfusion patterns (Jenkins, 2012). In addition, systemic effects of drugs should be considered, such as direct effects on blood vessels, which may lead to global effects that need to be considered in the analysis (Viviani et al., 2013).

Despite growing evidence that rCBF is altered by antipsychotic administration, its relationship with treatment response remains unclear. In fact, the few existing studies in this area have employed different methodologies, including positron emission tomography (PET), single-photon emission computed tomography (SPECT) and labelled-Xenon inhalation, and different design procedures (cross-sectional versus longitudinal). Achieving a better understanding of this relationship could help in the prediction of treatment outcomes and prognosis as well as in the identification of possible novel targets for antipsychotic action, while guiding decisions regarding how long an antipsychotic should be trialled for, or when an adequate dose is achieved (Lahti et al., 2009).

This systematic review aims to address three main questions: (1) is there consistent evidence that antipsychotic medications induce changes in global or regional rCBF; (2) if so, how do changes in rCBF correlate with symptoms prior to and following antipsychotic administration; and (3) do baseline rCBF differences predict the later response?

2. Methods

2.1. Data sources

Searches were performed in EMBASE, PsycINFO, and Medline databases for peer-reviewed articles published between January 1980 and March 2013. Search terms used were: [“schizophrenia” OR “psychosis” OR “schizo$”] OR [healthy controls” OR “normal volunteers” OR “controls”] AND [“neuroleptic agent” OR “atypical antipsychotic agent” OR “antipsychotic drug” OR “typical antipsychotic agent”] OR [“unmedicated” OR “antipsychotic-naïve”] AND [“Brain blood flow” OR “cerebral blood flow” OR “brain rCBF”] AND [“rest” OR “resting state” OR “baseline” OR “resting”]. Abstracts were reviewed to assess the relevance of the papers identified and any duplicates were removed. Further, references were also examined for relevance and included if appropriate.

2.2. Study selection

Studies were selected by the first author (R.G.) and checked by the second author (R.H.). Studies directly measuring resting cerebral blood flow (rCBF) in patients with a diagnosis of schizophrenia in relation to administration of an antipsychotic drug were

included. Task-related activation, metabolism, receptor function and electrophysiological studies were excluded. Papers comparing a medicated with an unmedicated group (cross-sectional) or using an 'on' and 'off' medication within-subjects design (longitudinal) were included. Only studies scanning at rest, with patients sitting or lying down, with eyes open or closed, were included. Proceedings from conferences were removed from the search.

2.3. Data extraction

For each study the following information was extracted, if available: (1) year of publication; (2) study design (cross-sectional, longitudinal single-dose or longitudinal multiple-dose); (3) participant demographics; (4) antipsychotic generation and dose; (5) duration of previous antipsychotic exposure; (6) duration of treatment prior to first scan and between first and second scans, if applicable; (7) image analysis strategy (region of interest, ROI, versus voxel-wise) and regions investigated; (8) rCBF quantification methodology and contrasts performed; (9) associations between rCBF values and symptomatology or treatment response. For all contrasts and associations, reported estimates of the strength of the effects were extracted when given (either Pearson's *r*, or Cohen's *d*). Where these were not reported but could be calculated from the data in the original paper, a Cohen's *d* effect size estimate was calculated using the methods outlined in Appendix A.

2.4. Analysis

There was insufficient homogeneity between studies to allow a quantitative, meta-analytic approach of region of interest studies. Therefore, a critical, systematic review was undertaken. Nevertheless, a subset of three VBM studies were subjected to signed differential mapping (SDM), a meta-analytic technique for voxel-wise neuroimaging data (Radua et al., 2013).

2.4.1. Study quality

Quality of papers included in the meta-analysis was scored in 6 key areas, as follows: (1) same scanner and sequence used for each subject (different scanner or sequence = 0, same scanner and sequence = 1); (2) patient group was antipsychotic-naïve (yes = 1, mixed group = 0.5, no = 0); (3) drugs administered according to a protocol for dose regime (yes = 1, no = 0); (4) drugs administered according to a protocol for duration (yes = 1, no = 0); (5) withdrawals explained (yes/none reported = 1, no = 0); (6) global rCBF controlled for in analysis (yes = 1, no = 0).

2.4.2. Signed Differential Mapping (SDM) meta-analysis

Signed differential mapping (SDM) is a voxel-based meta-analytic technique developed more recently than commonly used activation likelihood estimation (ALE) methods, and it has recently been used in a number of studies (Fusar-poli et al., 2012; Bora et al., 2011; Palaniyappan et al., 2012). Compared to ALE, it offers several advantages: it uses strict criteria to select coordinates, which avoids the bias of using regions identified with liberal thresholds; it weights for intra-study variance; and finally, it uses the general linear model allowing the use of covariates and comparisons between groups.

More specifically, SDM combines peak coordinates from published studies. The technique estimates an effect size map for each study from reported coordinates and weights each study by sample size. The pooled effect size at every voxel is calculated using standard meta-analytical methods. SDM requires that only studies reporting coordinates from a whole-brain voxel-wise analysis be included, discarding region of interest (ROI) studies. A meta-analysis of ROI studies was not possible due to a lack of homogeneity between these studies. The analysis was carried out using the SDM software freely available at http://www.sdmproject.com/ and full details of the technique can be found elsewhere (Radua et al., 2013).

We extracted and inputted into the SDM software the coordinates for brain regions showing significant rCBF increases or decreases at follow-up compared to baseline. We used default ES-SDM kernel size and thresholds (FWHM = 20 mm, voxel $P = 0.005$, peak height $z = 1$, cluster extent = 10 voxels), and carried out supplementary analyses including residual heterogeneity and jack-knife analyses to investigate the robustness of the results (Radua et al., 2012).

3. Results

We identified a total of 47 studies: 12 in unmedicated patients (Table 1), 10 cross-sectional (Table 2) and 25 longitudinal (Table 3).

3.1. Cross-sectional studies

To understand the effects of medications on the brain in disease, it is important to consider disease-related pathology, prior to treatment. Assessing the ways in which patients differ from healthy controls before they receive medication can help disentangle the differences in brain perfusion that are primary to the disorder from those that are a result of treatment. Therefore, we first review studies investigating rCBF in antipsychotic-naïve or unmedicated patients compared with healthy controls. We found 12 studies looking at unmedicated patients with schizophrenia. Four studies used a sample of antipsychotic-naïve patients and the remaining 8 used a mixture of antipsychotic-naïve and antipsychotic-free patients. Following this, we present findings from 11 studies comparing medicated and unmedicated patients with schizophrenia and healthy controls.

3.1.1. Studies investigating rCBF in unmedicated patients

Very few studies have investigated unmedicated patients, and even fewer have used antipsychotic-naïve patients. The latter would be most desirable to eliminate the possibility of identifying effects from long-term medication use, where patients undergo a washout of medication prior to scanning.

Two studies reported no differences in rCBF in schizophrenia compared with healthy controls (Günther et al., 1991; Steinberg et al., 1995b), although both found differences in task-activated rCBF. The other ten studies did report perfusion differences but the regions affected varied.

Eight studies reported findings in the frontal cortex, mostly in prefrontal, medial and orbital areas. Three studies reported hyperfrontality (Ebmeier et al., 1993; Catafau et al., 1994; Parellada et al., 1994) and five reported hypofrontality (Steinberg et al., 1995a; Vita et al., 1995; Andreasen et al., 1997; Kim et al., 2000; Scheef et al., 2010) in the patient group. Interestingly, studies reporting higher frontal rCBF more often recruited only antipsychotic-naïve patients, whilst those reporting lower frontal rCBF often had a mixed group. As suggested by some authors, these different results may support the hypothesis that hypofrontality is the result of chronicity, negative symptoms or long-term medication use, rather a primary correlate of the disease itself (Catafau et al., 1994).

Perfusion differences in the BG were also reported in several studies. Again, some reported higher rCBF (Early et al., 1987; Ebmeier et al., 1993) whilst others reported lower rCBF (Sheppard et al., 1983; Vita et al., 1995) in this region in patients. Other subcortical regions showed differences in patients with schizophrenia when compared with healthy controls, including the thalamus, which showed higher perfusion in three studies (Andreasen et al., 1997; Kim et al., 2000; Scheef et al., 2010).

Table 1
Cross-sectional studies in unmedicated patients with schizophrenia.

Reference	Participants (n) and interventions	Main findings
Sheppard et al. (1983)	*Antipsychotic-naïve* (6) *Antipsychotic-free* (6): 1–4 previous doses with day washout (4), 1–3 years with 7 day washout (2) *Healthy controls* (12)	No support for hypofrontality. ↓ rCBF in basal ganglia in patients ($d = 0.73$, $p < 0.05$).
Early et al. (1987)	*Antipsychotic-naïve* (10)	↑ rCBF in globus pallidus: whole brain ratio in patients ($p = 0.0056$).
Günther et al. (1991)	*Antipsychotic-naïve* (14) *Antipsychotic-free* (17): washout of between 1 week and 2 years *Healthy controls* (31)	No significant rCBF differences between patients and healthy controls.
Ebmeier et al. (1993)	*Antipsychotic-naïve* (10) *Antipsychotic-free* (10): washout of more than 2 weeks for oral and more than 2 months for depot *Healthy controls* (20)	↑ rCBF in frontal regions ($p < 0.05$) and right putamen in patients ($p < 0.05$). ↓ rCBF in left inferior anterior cingulate in patients ($p < 0.05$).
Catafau et al. (1994)	*Antipsychotic-naïve* (10) *Healthy controls* (8)	↑ rCBF in prefrontal cortex in patients (left: $p < 0.001$; right: $p < 0.05$).
Parellada et al. (1994)	*Antipsychotic-naïve* (6) *Healthy controls* (6)	↑ rCBF in prefrontal cortex in patients ($p < 0.05$)
Steinberg et al. (1995a)	*Antipsychotic-naïve* (7) *Antipsychotic-free* (9): washout of 8–365 days (median 30 days) *Healthy controls* (13)	↓ rCBF in "first break" patients compared with healthy controls in superior frontal, middle frontal and middle temporal regions ($p < 0.05$).
Steinberg et al. (1995b)	*Antipsychotic-naïve* (5) *Antipsychotic-free* (12): washout of more than 8 days *Healthy controls* (13)	No significant rCBF differences between patients and healthy controls.
Vita et al. (1995)	*Antipsychotic-naïve* (8) *Antipsychotic-free* (9): washout of more than 3 weeks *Healthy controls* (12)	Antipsychotic-naïve versus healthy controls: ↑ rCBF in cerebellum ($p < 0.05$), ↓ rCBF in putamen ($p < 0.05$), caudate ($p < 0.05$) and thalamus ($p < 0.003$). Antipsychotic-naïve versus antipsychotic-free: ↑ rCBF in cerebellum ($p < 0.05$), ↓ rCBF in putamen ($p < 0.05$), caudate ($p < 0.05$) and thalamus ($p < 0.05$).
Andreasen et al. (1997)	*Antipsychotic-naïve* (17) *Healthy controls* (17)	↑ rCBF in patients in left inferior frontal ($d = 1.26$), thalamus (left: $d = 1.12$; right: $d = 1.12$), retrosplinal cingulate (left: $d = 1.35$; right: $d = 1.56$), left parietal/supramarginal ($d = 1.46$), right fusiform/occipital ($d = 1.59$) and cerebellar regions (left: $d = 1.21$; right: $d = 1.36$). ↓ rCBF in patients in dorsolateral prefrontal (left: $d = 1.34$; right: $d = 1.22$), orbital frontal (left: $d = 1.18$; right: $d = 1.43$), middle frontal ($d = 1.18$), inferior temporal (left: $d = 1.27$; right: $d = 1.48$), mid cingulate ($d = 1.1$), precuneus ($d = 1.54$), left parietal ($d = 1.23$) and primary visual regions ($d = 1.58$).
Kim et al. (2000)	*Antipsychotic-free* (31): washout of 3 weeks *Healthy controls* (31)	↑ rCBF in patients in left frontal operculum ($d = 0.9$), cerebellum ($d = 1.48$), left thalamus ($d = 0.93$) and precentral regions (left: $d = 0.91$; right: $d = 0.81$). ↓ rCBF in patients in left middle frontal gyrus ($d = 0.98$), right inferior frontal gyrus ($d = 1.52$), left orbitofrontal ($d = 1.14$), anterior cingulate ($d = 0.93$), right insula ($d = 0.9$) and fusiform regions ($d = 0.97$).
Scheef et al. (2010)	*Antipsychotic-naïve* (8) *Antipsychotic-free* (3): washout of 2 weeks *Healthy controls* (25)	↑ rCBF in patients in thalamus, cerebellum and brainstem ($d = 2.82$), right parahippocampus ($d = 2.27$), amygdala (left: $d = 1.76$: right: $d = 1.34$), right precuneus ($d = 1.31$) and right occipital ($d = 1.27$). ↓ rCBF in patients in left and right parietal, frontal and anterior cingulate ($d = 3.09$), left inferior temporal gyrus ($d = 1.49$), cerebellum ($d = 1.47$), right middle temporal gyrus ($d = 1.25$) and left superior frontal gyrus (1.18).

Seven studies reported differences in temporal regions, all of which showed lower rCBF in patients as compared with healthy controls (Ebmeier et al., 1993; Catafau et al., 1994; Steinberg et al., 1995a; Vita et al., 1995; Andreasen et al., 1997; Kim et al., 2000; Scheef et al., 2010).

Interestingly, one study split their patient group according to previous antipsychotic exposure with 9 antipsychotic-naïve patients and 8 antipsychotic-free, who had undergone a washout of at least 3 weeks (Vita et al., 1995). Their results were revealing, with antipsychotic-naïve patients showing differences when compared with healthy controls in frontal, temporal and subcortical regions but antipsychotic-free patients showing no differences. This suggests that treatment with antipsychotic medication may make cerebral blood flow patterns in patients more similar to those of healthy controls, and that these effects may be long lasting even after withdrawal of medication.

These studies suggest that unmedicated patients with schizophrenia compared with controls show rCBF differences in frontal, temporal and BG regions. However, results are heterogeneous with the direction of difference (higher or lower rCBF in patients) varying between different studies. This heterogeneity may result from baseline differences in prior antipsychotic exposure and therefore caution should be taken when interpreting results from studies investigating the effects of medication.

3.1.2. *Schizophrenia patients versus healthy controls*

Nine studies compared patients and healthy controls. Only one of these separated patients according to medication status (medicated versus unmedicated) (Hook et al., 1995). The other eight compared patients as one group with healthy controls (Mathew et al., 1982, 1988; Gur et al., 1983, 1985; Geraud et al., 1987; Dousse et al., 1988; Paulman et al., 1990; Mori et al., 1999), making it difficult to disentangle the role of medication from that of illness. Two studies, both using 133-Xenon inhalation, reported lower global rCBF in patients with schizophrenia when compared to healthy controls (Mathew et al., 1982; Dousse et al., 1988).

More specific hemispheric and regional differences were also reported, although not always consistently. An early 133-Xenon inhalation study reported higher rCBF in the global left hemisphere compared with the right in patients but not in healthy controls (Gur et al., 1983, 1985). Mathew et al. (1988) reported more specifically that schizophrenia was associated with higher right occipital and

Table 2
Cross-sectional studies in patients and healthy controls; ↑ denotes higher rCBF; ↓ denotes lower rCBF.

Reference	Participants (n) and interventions	Correlations with clinical measures	Main findings
Medoff et al. (2001)	*Antipsychotic-treated* (10): 0.3 mg/kg/day Haloperidol *Antipsychotic-free* (18): 31 ± 17 days washout *Healthy controls* (12)	Correlations not explored	↑ rCBF in hippocampus in antipsychotic-free patients ($p < 0.05$).
Mori et al. (1999)	*Antipsychotic-treated* (118): type not reported, mean dose 1017.9 ± 1112.6 mg/day CP equivalents *Healthy controls* (21)	Correlations not explored	↑ antipsychotic dose associated with ↓ rCBF in the left middle cerebral artery region ($r = -0.167$, $p < 0.05$), left thalamus ($r = -0.231$, $p < 0.01$) and right thalamus ($r = -0.193$, $p < 0.05$).
Hook et al. (1995)	*Antipsychotic-treated* (15): type and dose not reported *Antipsychotic-free* (15): mixture of never treated, 4 week (oral medication) or 3 month (depot) washout *Healthy controls* (15)	Correlations not explored	Left hemisphere greater than right hemisphere flows ($d = 0.23$, $F = 0.386$, $p < 0.03$) and frontal greater than posterior flows ($d = 0.26$, $F = 0.480$, $p < 0.06$; trend to significance) in healthy controls and treated patients but not unmedicated patients.
Paulman et al. (1990)	*Antipsychotic-treated* (20): type and dose not reported *Antipsychotic-free* (20): one or two weeks washout *Healthy controls* (31)	Correlations not explored	↑ rCBF in right and left hemisphere ($d = 0.49$, $F = 4.01$, $p < 0.05$) and ↓ rCBF in left frontal and parietal and right frontal regions ($p < 0.05$) in patients compared with controls.
Goldstein et al. (1990)	*Antipsychotic-treated* (15): type not reported, mean dose 324 ± 341 mg/day CP equivalents *Healthy controls* (15)	Correlations not explored	↑ antipsychotic dose associated with ↓ global rCBF ($r = -0.34$, $p < 0.05$).
Dousse et al. (1988)	*Antipsychotic-treated* (24): type and dose not reported *Antipsychotic-free* (3): never treated *Healthy controls* (27)	Persistent visual hallucinations: temporal-occipital rCBF ($p < 0.02$)	No significant rCBF differences between treated and untreated patients. ↓ overall rCBF in patients compared with controls ($p < 0.02$).
Mathew et al. (1988)	*Antipsychotic-treated* (62): type not reported, mean dose 556.9 ± 872.9 mg/day CP equivalents *Antipsychotic-free* (46): two week washout *Healthy controls* (108)	Suspiciousness: Left temporal rCBF ($r = 0.26$, $p < 0.05$), right hemisphere antero-posterior gradient ($r = -0.25$, $p < 0.05$) Emotional withdrawal: Left parietal rCBF ($r = 0.25$, $p < 0.05$). Unusual thought content: Bilateral central rCBF (right: $r = 0.30$, left: $r = 0.27$, $p < 0.05$), bilateral parietal rCBF (right: $r = 0.31$, left: $r = 0.28$, $p < 0.05$), bilateral occipital rCBF (right: $r = 0.27$, left: $r = 0.33$, $p < 0.05$), right temporal rCBF ($r = 0.26$, $p < 0.05$), left frontal rCBF ($r = 0.29$, $p < 0.05$), right hemisphere antero-posterior gradient ($r = -0.28$, $p < 0.05$).	No significant rCBF differences between treated and untreated patients. ↑ right temporal and occipital, and left central, temporal and occipital rCBF in patients compared with controls ($d = 0.33$, $F = 2.86$, $p < 0.03$).
Geraud et al. (1987)	*Antipsychotic-treated* (29): type and dose not reported *Antipsychotic-free* (22): 13 never treated, 9 with 15 days (oral medication) or 45 days (depot) washout *Healthy controls* (36)	Correlations not explored	No significant rCBF differences between treated and untreated patients. 'Frontal pattern' significantly ↓ in patients ($d = 0.2$, $p < 0.01$) in patients.
Gur et al. (1983, 1985)	*Antipsychotic-treated* (17): Fluphenazine, Chlorpromazine, Thioridazine, Haloperidol, Thiothixene or Trifluoperazine, dose not reported *Antipsychotic-free* (19): 3 never treated, 5 not treated for one year, 3 not treated for two months, 8 with one week washout *Healthy controls* (44)	No significant relationships between CBF and clinical measures.	Medication x hemisphere x sex interaction ($d = 0.79$, $F[1,32] = 5.24$, $p = 0.29$). In men, ↓ left hemisphere flows and ↑ right hemisphere flows in anterior regions and ↑ flow bilaterally in posterior regions with antipsychotics. In women, ↑ flow bilaterally in anterior and posterior regions with antipsychotics.
Mathew et al. (1982)	*Antipsychotic-treated* (13): type and dose not reported *Antipsychotic-free* (9): one week washout *Healthy controls* (17)	Hallucinatory behaviour: Left parietal rCBF ($r = -0.44$, $p < 0.02$), temporal rCBF ($r = -0.35$, $p < 0.05$), right temporoparietal rCBF ($r = -0.38$, $p < 0.04$), occipital rCBF ($r = -0.41$, $p < 0.04$).	No significant rCBF differences between treated and untreated patients.

left parietal rCBF than controls in a large group of over 200 patients and healthy controls.

Findings were more consistent across frontal regions. Comparing values averaged across frontal regions with those averaged across temporal, parietal and occipital regions, Mathew et al. (1988) identified a significantly lower anterior to posterior ratio in the patient group than in controls, indicating frontal hypoperfusion. Consistent with this, Geraud et al. (1987) reported a non-significant trend for lower frontal flow (as a ratio of flow in the rest of the brain) in patients with schizophrenia than in controls. Also, Paulman et al. (1990) reported bilateral frontal and temporal hypoperfusion in patients compared with controls. These authors suggested that

Table 3
Longitudinal studies in patients and healthy controls; ↑ denotes higher rCBF; ↓ denotes lower rCBF.

	Reference	Participants (*n*) and medication	Correlations	Main findings
Studies in healthy controls	Fernández-Seara et al. (2010)	*Healthy controls* (18): 10 mg metoclopramide; placebo across two visits	N/A	↑ rCBF in striatum, particularly the putamen (left: $d = 0.61$, $p = 0.003$; right: $d = 0.57$, $p = 0.031$) and the thalamus (left: $d = 0.56$, $p = 0.009$; right: $d = 0.57$, $p = 0.007$), ↓ rCBF in insula ($d = 1.57$) and anterior temporal lobe ($d = 1.07$).
	Handley et al. (2012)	*Healthy controls* (20): 3 mg haloperidol; 10 mg aripiprazole; placebo randomised across three visits	N/A	Haloperidol versus placebo: ↑ rCBF in putamen ($d = 2.83$, $p < 0.0001$) and precentral gyrus ($d = 1.74$, $p < 0.0001$) and ↓ rCBF in inferior temporal gyrus ($d = 2.01$, $p < 0.0001$). Aripiprazole versus placebo: ↑ rCBF in claustrum ($d = 2.01$, $p < 0.0001$), putamen ($d = 1.83$, $p = 0.002$), and anterior cingulate ($d = 1.68$, $p = 0.006$). ↓ rCBF in posterior cingulate ($d = 1.86$, $p = 0.001$), prefrontal cortex ($d = 1.67$, $p = 0.025$), superior parietal lobe ($d = 1.62$, $p = 0.025$) and orbitofrontal cortex ($d = 1.35$, $p = 0.039$). Haloperidol > Aripiprazole: putamen ($d = 1.77$, $p = 0.002$).
	Viviani et al. (2013)	*Healthy controls* (20): 100 mg BD amisulpride for 7 days; placebo double-blind with two week washout between scans	N/A	↑ rCBF in putamen (trend: $d = 0.43$, $p = 0.09$). ↓ rCBF in widespread frontal regions, including anterior cingulate ($d = 2.57$, $p = 0.01$).
Single-dose	Lahti et al. (2005)	*Patients* (12): 10 mg Haloperidol (6), 15 mg Olanzapine (6); all previously treated, unmedicated for two weeks prior to scan *Healthy controls* (0)	Correlations not explored	Haloperidol: ↑ rCBF in left caudate ($z = 5.83$), ↓ rCBF in medial frontal cortex ($z = 5.37$), middle temporal cortex ($z = 5.33$) and left cerebellum ($z = 4.91$). Olanzapine: ↑ rCBF in right middle temporal cortex ($z = 4.42$) and anterior cingulate ($z = 4.76$), ↓ rCBF in lingual cortex ($z = 4.42$).
	Goldman et al. (1996)	*Patients* (8): 5 mg Haloperidol; all previously treated, unmedicated for at least two weeks prior to scan *Healthy controls* (9): 5 mg Haloperidol	Correlations not explored	Patients: no significant rCBF changes. Controls: ↑ global rCBF ($F = 5.53$, $p < 0.05$).
	Jibiki et al. (1990–1991)	*Patients* (2): 0.08 mg/kg IM Haloperidol; previous antipsychotic exposure not reported *Healthy controls* (2): 0.08 mg/kg IM Haloperidol	Correlations not explored	Patients: 1/2 exhibited widespread ↓ rCBF across bilateral cerebral hemispheres. Controls: 1/2 exhibited widespread ↓ rCBF across bilateral cerebral hemispheres.
	Matsuda et al. (1990)	*Patients* (3): 5 mg IM Haloperidol; all previously treated *Healthy controls* (2): 5 mg IM Haloperidol	Correlations not explored	Patients: Left-sided dominance becomes right-sided dominance and ↑ frontal-to-other ratios in all areas apart from the striatum. Controls: Similar alterations to those in patients but of a smaller magnitude. (Details regarding statistical analysis or significance not provided)

Table 3 (*Continued*)

	Reference	Participants (*n*) and medication	Correlations	Main findings
	Ertugrul et al. (2009)	*Patients* (22): Clozapine for 8 weeks, mean daily dose 350 ± 234.52 mg/day CP equivalents; all previously treated and treatment resistant *Healthy controls* (0)	Correlations not explored	↑ baseline rCBF in right frontal and thalamus of responders. At follow-up, ↑ rCBF in right ($d = 1.35$, $p = 0.007$) and left ($d = 1.20$, $p = 0.013$) (superior and medial) frontal to caudate; trend to significant ↑ rCBF in right ($d = 1.05$, $p = 0.018$) and left ($d = 1.12$, $p = 0.029$) frontal to caudate rCBF in responders. No significant changes in responders.
Multiple dose	Lahti et al. (2009)	*Patients* (29): Haloperidol or Olanzapine for 6 weeks, mean daily dose 10.43 ± 3.3 mg and 15.9 ± 4.8 mg respectively; all previously treated, medication free for 2 weeks *Healthy controls* (0)	Correlations not explored	↑ rCBF in left pre-central ($t = 4.58$, $p = 0.022$) and post-central cortex ($t = 4.42$, $p = 0.047$) and ↓ rCBF in anterior cingulate cortex ($t = 5.60$, $p < 0.0001$) following treatment. Responders had ↑ rCBF in right ventral striatum ($t = 5.86$, $p = 0.005$) with Haloperidol. Responders to Olanzapine had ↑ rCBF in cerebellum ($t = 4.92$, $p = 0.012$) and right ventral putamen ($t = 4.78$, $p = 0.001$) but ↓ rCBF in sensorimotor ($t = 6.32$, $p < 0.0001$), middle frontal ($t = 4.88$, $p = 0.003$), superior parietal ($t = 4.71$, $p = 0.002$) and medial frontal ($t = 4.91$, $p = 0.001$) regions.
	Sharafi (2005)	*Patients* (20): Clozapine or 'other classical antipsychotic', duration not reported, mean 300 mg/day and 600 mg/day CP equivalents respectively; previously treated, medication free for 3 months *Healthy controls* (0)	*Baseline* Paranoia: Left temporal rCBF ($r = 0.50$). *Follow-up* Anergia: Posterior parietal rCBF ($r = -0.50$ to -0.53) Thought disturbance: Left superior frontal rCBF ($r = -0.71$), Left thalamic/basal ganglia rCBF ($r = 0.55$) Paranoia: Left superior frontal rCBF ($r = -0.68$) Depression: Right superior temporal rCBF ($r = -0.55$).	Patients had ↓ rCBF in superior frontal ($p < 0.001$), inferior frontal ($p < 0.01$), temporal ($p < 0.022$), posterior parietal ($p < 0.001$) and anterior parietal ($p < 0.002$) regions at baseline. Patients had ↓ rCBF in superior frontal ($p < 0.008$), inferior frontal ($p < 0.043$), posterior parietal ($p < 0.001$) and right anterior parietal ($p = 0.013$) regions at follow-up.
	Novak et al. (2005)	*Patients* (9): Fluphenazine, Olanzapine or Risperidone, for median 9 weeks, dosages not reported; all antipsychotic-naïve *Healthy controls* (0)	No significant correlations.	↑ rCBF in upper left dl PFC ($d = 0.67$, $p < 0.05$) and upper right dl PFC ($d = 0.83$, $p < 0.05$) following treatment.
	Lahti et al. (2003)	*Patients* (6): Haloperidol (for 12 ± 10 weeks) or Clozapine (for 23 ± 12 weeks), daily doses 12 ± 4.5 mg and 280 ± 135 mg respectively; all previously treated, medication free for mean 19.2 ± 4.8 days *Healthy controls* (0)	Correlations not explored	↑ rCBF in right ventral striatum ($t = 4.38$), left caudate ($t = 4.04$), dorsolateral frontal (right: $t = 4.09$; left: $t = 3.39$) and left sensory motor ($t = 4.01$) regions and ↓ rCBF in left hippocampus ($t = 3.96$), left insula ($t = 3.34$), ventrolateral frontal (right: $t = 3.28$; left: $t = 4.22$) and right middle temporal region ($t = 3.26$) following treatment.
	Vaiva et al. (2002)	*Patients* (19): low-dose Amisulpride for 4 weeks, 100 mg/day; 9/19 previously treated, medication free for 6 weeks, 10/19 antipsychotic-naïve *Healthy controls* (0)	*Follow-up* Affective withdrawal improvements: posterior frontal rCBF ($r = 0.46$ to 0.48, $p < 0.054$), temporo-parietal junction rCBF ($r = 0.5$, $p = 0.034$) Anhedonia improvements: Antero-internal frontal rCBF ($r = -0.51$, $p = 0.003$)	↑ rCBF in dlPFC ($d = 0.4$, $p < 0.002$) and right posterior frontal cortex ($d = 0.22$, $p = 0.007$) following treatment.
	Corson et al. (2002)	*Patients* (29): Haloperidol or Risperidone, for mean 27 days, all antipsychotic-naïve *Healthy controls* (29): no intervention, scanned only at baseline	Correlations not explored	Analysis of a subset of 13 patients showing ↑ rCBF in caudate (left: $d = 0.17$; right: $d = 0.70$, $p < 0.009$) and putamen (left: $d = 0.22$; right: $d = 0.25$, $p < 0.041$) following treatment.

Miller et al. (2001)	*Patients* (32): Haloperidol or Risperidone for 3 weeks, mean daily doses 11.2 ± 5.0 mg and 4.9 ± 2.8 mg respectively; 15/32 previously treated, 17/32 antipsychotic-naïve *Healthy controls* (0)	Correlations not explored	↑ rCBF in left putamen (t = 3.0) and left posterior cingulate gyrus (t = 4.1) and ↓ rCBF in left dl PFC (t = 3.2), left frontal regions (t = 3.3), right straight gyrus (t = 3.7) and left insular (t = 3.00) following Haloperidol. ↓ rCBF in the left (t = 4.9/3.2) and right (t = 2.9) cerebellum following Risperidone.
Yildiz et al. (2000)	*Patients* (15): Haloperidol for one month, dosage dependent on clinical status of patient; 6-15 previously treated, medication free for 1 month, 9/15 antipsychotic-naïve *Healthy controls* (10): no intervention, scanned only at baseline	No significant correlations.	Patients had ↓ baseline rCBF in left inferior temporal (d = 2.39, p < 0.05) and left superior temporal (d = 1.43, p < 0.05) regions than controls. Following treatment, patients had ↓ rCBF in left inferior temporal (d = 0.68) and left superior temporal (d = 1.07) regions than controls.
Livingston et al. (1998)	*Patients* (27): Haloperidol or Risperidone for six months, dosages not reported, all antipsychotic-naïve *Healthy controls* (38): no intervention, scanned only at baseline	No significant correlations.	↑ rCBF in left putamen (p = 0.0001, mean difference = 6.17) and right putamen (p = 0.004), and ↓ rCBF in left inferior lateral frontal (p = 0.006) and right inferior calcerine (p = 0.02) regions following treatment.
Erkwoh et al. (1997)	*Patients* (24): various antipsychotics (types not specified), duration not reported, mean dose 616 mg/day CP equivalents, all antipsychotic-naïve *Healthy controls* (20): patients examined for small meningiomas, no intervention, scanned only at baseline	*Baseline* Delusions: Anterior cingulate cortex rCBF (r = −0.60) Formal thought disorder: Inferior frontal rCBF (r = 0.64–0.68), left superior temporal rCBF (r = 0.62) Grandiosity: Inferior frontal rCBF (0.60 to 0.62), right inferior temporal rCBF (r = 0.68) Persecution: Inferior frontal rCBF (r = −0.61 to −0.62), superior left temporal rCBF (−0.64) Stereotyped thoughts: Left superior temporal rCBF (r = −0.66), left parietal rCBF (r = −0.61) *Follow-up* Blunted affect: Left thalamic rCBF (r = −0.62) Emotional withdrawal: Left basal ganglia rCBF (r = −0.60) Difficulties in abstract thinking: Anterior cingulate rCBF (r = −0.62), right basal ganglia rCBF (r = −0.61), right thalamic rCBF (r = −0.62) Lack of spontaneity: Left mesial temporal rCBF (r = −0.62) Stereotyped thoughts: Inferior temporal rCBF (r = −0.62 to −0.63), left mesial temporal rCBF (r = −0.61).	At baseline patients showed↓ rCBF in bilateral inferior frontal (p < 0.05), left superior temporal (p < 0.05) and left superior temporal (p < 0.05) regions compared with controls. At follow-up patients showed ↓ rCBF in left inferior frontal regions (p < 0.05) compared with controls.
Rodriguez et al. (1997)	*Patients* (39): Clozapine, mean dose 551 mg/day for six months, all previously treated, sample includes 24 patients from previous study *Healthy controls* (0)	Correlations not explored	Responders had ↑ rCBF in thalamus (t = 4.66, p = 0.00003), basal ganglia (left: t = 4.12, p = 0.0002; right: t = 3.28, p = 0.002), left lower prefrontal cortex (t = 2.98, p = 0.005) and right upper prefrontal cortex (t = 3.14, p = 0.003) at baseline. In responders there was ↓ rCBF in thalamus (t = 3.05, p = 0.009), basal ganglia (right: t = 3.31, p = 0.005; left: t = 4.13, p = 0.001), upper dorsolateral cortex (left: t = 2.67, p = 0.019; right: t = 2.52, p = 0.025), and anterior prefrontal cortex (left: t = 3.18, p = 0.007; right: t = 2.79, p = 0.015) following treatment. Non-responders showed no significant changes.
Miller et al. (1997b)	*Patients* (33): Clozapine, Haloperidol and others, time between scans – 3 weeks; 25/33 previously treated, 8/33 antipsychotic-naïve *Healthy controls* (0)	No significant correlations.	↑ rCBF in left basal ganglia (p < 0.01) following treatment.

Table 3 (*Continued*)

	Reference	Participants (*n*) and medication	Correlations	Main findings
	Miller et al. (1997a)	*Patients* (17): Clozapine, Haloperidol, Loxitane, Olanzapine, Risperidone, Thiothixene or Trifluoperazine, time between scans – 3 weeks; 14/17 medication free for 3 weeks, 3/17 medication-naïve *Healthy controls* (0)	Correlations not explored	(Order of scans differed between patients therefore results reported for on- and off-medication states) Whilst off medication patients had ↓ rCBF in anterior cingulate cortex ($d = 0.57$), left dorsolateral frontal cortex ($d = 0.36$), inferior frontal cortex ($d = 0.50$) and bilateral cerebellum (left: $d = 0.49$, right: $d = 0.49$). On medication patients had ↑ rCBF in left basal ganglia ($d = 0.22$) and left fusiform gyrus ($d = 0.5$).
	Sabri et al. (1997)	*Patients* (24): Bromperidol, Clozapine, Haloperidol, Levomepromazine, sulpiride or thioridazine, 848.7 mg/day CP equivalents over an average of 96.8 days; all antipsychotic-naïve *Healthy controls* (20): no intervention, scanned only at baseline	*Baseline* Sum positive score: Frontal, cingulate and left temporal rCBF ratios ($r = 0.30$) Sum negative scores: Frontal, cingulate and temporal rCBF ratios ($r = -0.30$) Delusional ideas, hallucinatory behaviour and suspiciousness: Bifrontal, cingulate, left temporal and left thalamic rCBF ratios ($r = -0.59$ to -0.66, $p < 0.001$ to $p < 0.0005$) Formal thought disorder and grandiosity: Bifrontal and bitemporal rCBF ratios ($r = 0.59$ to 0.70, $p < 0.001$ to $p < 0.0005$) Stereotyped ideas: Left frontal, cingulate, left parietal and left temporal rCBF ratios ($r = -0.59$ to -0.65, $p < 0.001$ to $p < 0.0005$) *Follow-up* Sum negative score: Frontal, cingulate, temporal, basal ganglia and thalamic rCBF ratios ($r = -0.59$ to -0.80, $p < 0.001$ to $p < 0.0005$). Affective flattening and emotional withdrawal: Frontal, temporal, basal ganglia and thalamic rCBF ratios ($r = -0.59$ to $r = -0.67$, $p < 0.001$). Difficulties with abstract thinking: Right frontal, cingulate, basal ganglia and thalamic rCBF ratios on the right ($r = -0.63$ to -0.74, $p < 0.001$ to $p < 0.0005$). Decreased spontaneity and stereotyped thinking: Bitemporal rCBF ratios ($r = -0.59$ to -0.71, $p < 0.001$ to $p < 0.0005$).	Paranoid subgroup of patients had ↑ baseline rCBF in left parietal ($d = 1.25$, $p < 0.05$), left basal ganglia ($d = 1.00$, $p < 0.025$) and right basal ganglia ($d = 1.00$, $p < 0.025$) compared with controls. They also showed ↑ baseline rCBF in left inferior frontal ($d = 1.95$, $p < 0.025$) and right inferior frontal ($d = 1.33$, $p < 0.025$) regions compared to non-paranoid patients. Following treatment, the paranoid subgroup showed ↓ rCBF in left inferior frontal regions ($d = 1.41$, $p < 0.025$).
	Rodriguez et al. (1996)	*Patients* (24): 600 mg/day Clozapine for six months; all previously treated *Healthy controls* (0)	No significant correlations.	Non-responders had ↓ rCBF in thalamus ($d = 1.85$, $p < 0.05$), left basal ganglia ($d = 1.34$, $p = 0.001$) and right prefrontal cortex ($d = 1.40$, $p = 0.001$) than responders at baseline. Following treatment, responders had↓ rCBF – left basal ganglia ($d = 1.59$, $p < 0.05$) and thalamus ($d = 1.25$, $p < 0.05$) but non-responders showed no significant rCBF changes.
	Warkentin et al. (1990)	*Patients* (17; 10 measured at baseline and follow up): Haloperidol, Flupenthixol, Perphenazine, Thioridazine or Zuclopenthixol, duration not reported; 6/10 medication free for 3–12 months, 4/10 medication-naïve *Healthy controls* (10): no intervention, scanned only at baseline	*Baseline* 'Greater behavioural disturbance': Right frontal to occipital rCBF ratio ($r = 0.916$, $p < 0.001$), right frontal to parietal rCBF ratio ($r = 0.946$, $p < 0.0001$), frontal rCBF ($r = 0.905$, $p < 0.002$), parietal rCBF ($r = -0.881$, $p < 0.004$).	↓ rCBF in left frontal-occipital ratio ($t = 3.403$, $p < 0.01$) with left frontal-occipital ratio significantly lower than right ($t = 2.661$, $p < 0.03$) following treatment.

these differences may be related to cognitive function, as left hypofrontality was associated with neuropsychological impairments on the Wisconsin Card Sorting Task (WCST). The authors also suggested that specific patterns may be related to particular symptom complexes, finding greater frontal deficits in paranoid patients compared with greater temporal deficits in non-paranoid patients.

Mori et al. (1999) assessed rCBF using Xenon-enhanced computed tomography in 118 patients and 21 controls, reporting significantly smaller rCBF in all regions investigated (bilateral putamen, bilateral thalamus and regions around the anterior middle and posterior cerebral artery) apart from one (right posterior cerebral artery region).

The only study that compared medicated ($n = 15$) and unmedicated patients ($n = 15$) separately with 15 controls (Hook et al., 1995) found that healthy controls and medicated, but not unmedicated, patients with schizophrenia had higher rCBF in frontal than other regions, and higher left than right hemisphere rCBF, particularly in frontal areas. In contrast, unmedicated patients had a tendency to greater right than left hemisphere rCBF in frontal regions, suggesting that medication may lead to perfusion patterns more similar to those of healthy controls. Interestingly, medicated and unmedicated patient groups did not differ on clinical measures, which may reflect an underrepresentation of more severely symptomatic patients.

Taken together the above cross-sectional studies suggest the presence of baseline reductions in global rCBF in patients with schizophrenia and provide some support for hypofrontality in schizophrenia. However, most did not divide patients into those medicated and unmedicated, leaving the precise role played by antipsychotics on rCBF differences unclear.

3.1.3. Medicated schizophrenia versus unmedicated schizophrenia

Seven studies directly compared medicated and unmedicated patients with schizophrenia, with five reporting no global or regional rCBF differences (Mathew et al., 1982, 1988; Gur et al., 1983, 1985; Geraud et al., 1987; Dousse et al., 1988; Paulman et al., 1990; Medoff et al., 2001).

Two studies found an effect of medication on rCBF. Gur et al. (1983, 1985) reported an interaction between medication (a variety of naturalistically prescribed drugs, dose not stated), sex and hemisphere. In men, higher rCBF was seen in the anterior right hemisphere and posterior bilateral regions in those medicated than those unmedicated. Women showed higher bilateral rCBF both anteriorly and posteriorly when medicated, but more specific brain regions were not identified.

Medoff et al. (2001) used PET $[^{15}O]H_2O$ to compare 10 haloperidol-treated (0.3 mg/kg/day) with 18 unmedicated patients (mean wash-out 31 ± 17 days). They reported higher hippocampal rCBF in the unmedicated than in the medicated group. Interestingly, it has recently been reported that hippocampal perfusion may be 'normalised' or reduced following antipsychotic treatment (Tamminga et al., 2012).

The remaining five studies did not find rCBF differences between medicated and unmedicated patients. Of note, there was great heterogeneity in illness duration, medication type and exposure (duration and dosage). Interestingly, negative studies had usually implemented short wash-out periods (less than two weeks), leaving open the possibility that antipsychotic effects could have been still present. One cross-sectional study included medication-naïve patients, and also reported no differences compared to treated patients. However, the sample size was so small ($n = 3$) that it may have lacked statistical power (Dousse et al., 1988). Instead, longitudinal studies of antipsychotic-naïve patients provide a more powerful design to investigate potential effects.

3.1.4. Effects of dosage

Two cross-sectional studies evaluated the effect of antipsychotic dose on rCBF. Goldstein et al. (1990) reported that higher dosage was associated with lower global rCBF in 15 patients. In a larger sample of 118 patients with schizophrenia, Mori et al. (1999) reported that a higher dose was associated with lower rCBF in the thalamus. These studies suggest that there may be a dose-response relationship in rCBF changes and that dosage is an important variable to consider in the interpretation of brain imaging studies.

3.2. Longitudinal studies

Longitudinal studies conducted over varying time intervals may be more informative than cross-sectional designs on the direction of causality. The inclusion of healthy controls allows for between-subjects analyses, providing supplementary information on areas affected by treatment independently of any underlying pathophysiology. It also helps clarifying whether any longitudinal rCBF change in patients represents normalisation, overcompensation or continued abnormality. Studies in healthy controls can provide information regarding the neurobiological changes elicited by antipsychotics, without the confound of potential disease-related pathology. However, to our knowledge only three studies investigating rCBF changes related to antipsychotic drugs in healthy controls have been published. These are reviewed briefly below. Following this, we present findings from 21 longitudinal studies of patients, 4 of which administered a single-dose of antipsychotic and 17 of which administered multiple-doses of antipsychotic medication.

3.2.1. Studies in healthy controls

In a longitudinal, placebo-controlled study, Fernández-Seara et al. (2010) looked at the effects of a single 10 mg oral dose of metoclopramide (a dopamine D2 antagonist) in a group of 18 healthy controls using arterial spin labelling (ASL). Using voxel-wise and ROI approaches they found increases in the striatum, particularly the putamen, as well as the thalamus. Meanwhile, decreased perfusion was seen in the insula and anterior temporal lobe. Our group (Handley et al., 2012) used ASL to investigate the effects of single-dose haloperidol (3 mg) or aripiprazole (10 mg) on rCBF using a placebo-controlled, repeated measures design in a group of 20 healthy males. We found that both drugs were associated with significant rCBF increase in putamen and anterior cingulate when compared with placebo. Aripiprazole was also associated with rCBF decrease in several regions, including the posterior cingulate, superior frontal and superior parietal areas. Finally, a third study looked at low-dose amisulpride in 20 healthy men and found an increase in putamen perfusion, albeit at a trend level (Viviani et al., 2013). They also reported widespread decreases in frontal cortical regions and the anterior cingulate.

The very few studies that have been carried out in healthy controls suggest that antipsychotics may be associated with increased perfusion in the striatum and other subcortical regions, and decreased perfusion in cortical regions. However, different antipsychotics appear to induce different patterns of perfusion change and therefore dose, type and duration of treatment are all important considerations when interpreting results.

3.2.2. Single-dose studies

Four studies reported on rCBF minutes or hours after a single-dose of haloperidol or olanzapine (Jibiki et al., 1990–1991; Matsuda et al., 1990; Goldman et al., 1996; Lahti et al., 2005).

A small study used 99mTcHMPAO SPECT in two unmedicated patients and two healthy controls before and after a single dose of 0.08 mg/kg IM haloperidol and found hemispheric perfusion

reduction in one patient and one control but little or no effect in the others (Jibiki et al., 1990–1991).

Another study administered 5 mg IM haloperidol to three patients with schizophrenia and two healthy controls (Matsuda et al., 1990). Post-treatment all subjects showed increased frontal-to-temporal, frontal-to-parietal and frontal-to-occipital ratios, more extensive in patients. No change was found in the frontal-to-striatal ratios. Patients also changed from higher left-than-right rCBF in all cortical areas at baseline to higher right-than-left rCBF following haloperidol. Of note, no test for significance was reported for these changes.

The largest study used PET $[^{15}O]H_2O$ in 12 patients with schizophrenia administered a single-dose of either 10 mg haloperidol or 15 mg olanzapine (Lahti et al., 2005). Both antipsychotics were associated with an increase in rCBF in the caudate (as well as differential effects as below).

Finally, one study failed to find any rCBF changes after administration of 5 mg haloperidol in patients with schizophrenia, but reported increased global rCBF in controls (Goldman et al., 1996). It is possible that acute effects are not seen in individuals chronically exposed to antipsychotics after a wash-out period of two weeks. Inconsistencies may also be explained by Goldman's use of ^{133}Xenon inhalation to gain crude global measures of rCBF as opposed to the voxel-by-voxel analysis of PET used by Lahti's group. Additionally, Goldman's group investigated changes over three hours whereas Lahti's group considered individual drug pharmacokinetics to capture changes, incorporating the plasma Tmax, which may further explain some of these inconsistencies.

Longitudinal single-dose studies suggest an effect of antipsychotics on brain physiology within hours of administration. However, changes in clinical measures are not seen within hours of antipsychotic administration and so cannot be investigated by acute studies. In addition, these few studies, with small, heterogeneous samples and variable methodologies make it difficult to draw conclusions.

3.2.3. Multiple-dose studies

Seventeen studies assessed rCBF longitudinally, before and after treatment lasting between three weeks to six months, and are discussed here. Studies that divided patients according to treatment response are discussed later.

3.2.3.1. Pre- and post-treatment scans within patients. Eleven longitudinal studies reported within group pre- and post-treatment rCBF changes in patients with schizophrenia (Warkentin et al., 1990; Sabri et al., 1997; Rodriguez et al., 1996, 1997; Miller et al., 1997a, 1997b, 2001; Livingston et al., 1998; Corson et al., 2002; Lahti et al., 2003; Novak et al., 2005).

Seven studies identified frontal perfusion changes following antipsychotic treatment. Two reported an increase in perfusion in the dorsolateral prefrontal cortex and inferior frontal regions following several weeks of treatment in previously antipsychotic-naïve patients (Sabri et al., 1997; Novak et al., 2005). In contrast, two studies reported decreased frontal rCBF following treatment (Warkentin et al., 1990; Livingston et al., 1998). Interestingly, Miller et al. (1997a, 1997b, 2001) reported increases in frontal perfusion following withdrawal from antipsychotics.

Sample heterogeneity and methodological differences (including location and extent of regions investigated, imaging modality and previous antipsychotic exposure in addition to antipsychotic type) may account for these inconsistencies (Marco et al., 1997). Alternatively, hypofrontality may be associated only with certain subtypes of schizophrenia. Consistent with this, frontal rCBF increases after treatment have been reported in paranoid patients (Sabri et al., 1997) and in those with prominent negative symptoms and poor treatment response (Vaiva et al., 2002).

Changes in rCBF have also been reported in the BG. Five reported increased rCBF following both first and second generation antipsychotics (Livingston et al., 1998; Miller et al., 1997a, 1997b, 2001; Corson et al., 2002; Lahti et al., 2003). However, one study reported a decrease in rCBF following a switch from 'classical' antipsychotics to clozapine, indicating differential effects in this region (Rodriguez et al., 1996, 1997). Three studies did not report rCBF changes in the BG at all following antipsychotics (Vaiva et al., 2002; Novak et al., 2005; Ertugrul et al., 2009).

Evidence for perfusion changes in temporal regions has been inconsistent. One study showed hyperperfusion of the temporal lobe, which changed to be more similar to that of healthy controls following treatment (Sabri et al., 1997). Increased fusiform gyrus rCBF was seen following treatment in a pilot but not in a larger follow-up study (Miller et al., 1997b, 2001). Lahti et al. (2009) found decreased rCBF in various temporal regions following treatment with haloperidol. Further divisions of the temporal lobe may elucidate a more complicated pattern of rCBF changes associated with treatment.

In summary, within-subjects comparisons suggest an association between antipsychotic administration and frontal perfusion changes, although the direction of change may depend on the subregion or even the subtype of schizophrenia investigated. The most consistent finding in these studies is the increase in BG rCBF following treatment. The inclusion of a control group might help elucidate which patterns of abnormality are associated with the disorder.

3.2.3.2. Pre- and post-treatment scans in patients compared with single scan in healthy controls. Six studies compared pre- and post-treatment rCBF in patients with schizophrenia with healthy control scans taken at a single time point (Warkentin et al., 1990; Erkwoh et al., 1997; Sabri et al., 1997; Livingston et al., 1998; Yildiz et al., 2000; Corson et al., 2002).

Results for frontal regions have varied. In a group of 27 antipsychotic-naïve patients, hypofrontality was evident before treatment in medial frontal regions and remained evident following six months of haloperidol or risperidone (Livingston et al., 1998). Erkwoh et al. (1997) found lower frontal rCBF in patients compared with controls at baseline that, however, only remained evident in the left hemisphere following treatment with various antipsychotics. In contrast, Warkentin et al. (1990) found lower left frontal-occipital rCBF ratios in patients following treatment only.

Interestingly, another study reported hypofrontality in some patients ($n = 3$) but hyperfrontality in others ($n = 9$) at baseline compared with healthy controls (Sabri et al., 1997). At follow-up, two-thirds of subjects in each group had perfusion values similar to those of controls, with the other third showing only a tendency to similar values. The subgroup of patients with paranoid symptoms at baseline had higher parietal and BG rCBF than healthy controls, and higher inferior frontal rCBF than paranoid-hallucinatory patients. Following treatment, rCBF in this region decreased in the paranoid subgroup.

Two multiple-dose longitudinal studies reported increased BG rCBF following antipsychotics (Corson et al., 2002; Livingston et al., 1998). Interestingly, Corson et al. (2002) did not find differences in BG rCBF between antipsychotic-naïve and healthy controls at baseline, supporting the notion that some rCBF alteration in this brain region may be underpinned by antipsychotic action.

Differences in rCBF have also been reported in temporal regions. Fifteen patients (six with one month antipsychotic wash-out and nine antipsychotic-naïve) showed lower rCBF in left superior and inferior temporal regions compared with ten controls both at baseline and follow-up (Yildiz et al., 2000). Previous antipsychotic exposure may have masked some alterations. Indeed, another study in antipsychotic-naïve patients showed that lower superior

temporal regions perfusion seen at baseline in patients disappeared following antipsychotic treatment (Erkwoh et al., 1997).

In summary, longitudinal studies provide more robust evidence of changes following treatment, but are subject to similar methodological criticisms as cross-sectional studies, including heterogeneity in prior antipsychotic exposure, illness chronicity, clinical presentation and methodology. Nevertheless, rCBF in BG and frontal regions appears to be affected by treatment, whilst evidence is less consistent for temporal regions.

3.3. Differential effects of antipsychotics

Elucidating areas of commonality and difference by controlled comparison of different antipsychotics may allow drug-specific clinical effects to be attributed to regional brain effects. We found six studies directly comparing antipsychotics: three compared haloperidol and a SGA other than clozapine (Corson et al., 2002; Miller et al., 2001; Lahti et al., 2009), three compared FGAs with clozapine (Lahti et al., 2003, 2005; Sharafi, 2005).

A ROI study investigated caudate and putamen perfusion, reporting no differences between haloperidol and risperidone administered for approximately four weeks (Corson et al., 2002). However, participants were prescribed relatively high doses of risperidone (mean 5.5 mg/day) at which the drug may act similarly to FGAs (Nyberg et al., 1999). Indeed, four studies reported that FGAs are associated with greater striatal rCBF increases (Miller et al., 2001; Lahti et al., 2003, 2005, 2009), which may also explain their different side effect profiles (Davis et al., 2005; Vita and De Peri, 2007).

Cortical areas also demonstrate susceptibility to antipsychotic-generation specific effects. One study reported greater frontal decreases with FGAs (Miller et al., 2001), with SGAs associated with greater increases in frontal, parietal, temporal and occipital cortical rCBF (Lahti et al., 2003, 2005, 2009; Sharafi, 2005).

Antipsychotic generation should therefore be considered when investigating treatment effects on brain physiology.

3.4. rCBF and clinical measures

Although most studies reported measures of symptomatology, these were not always related to measures of resting rCBF before or after treatment.

3.4.1. Cross-sectional studies

Five cross-sectional studies correlated rCBF with symptom scores, some finding none significant (Gur et al., 1983, 1985). Mathew et al. (1988) reported small positive correlations between total Brief Psychiatric Rating Scale (BPRS) and parietal, central and temporal rCBF whilst Paulman et al. (1990) reported mean positive symptom scores moderately positively correlated with absolute right and left hemisphere flows, whilst negative symptom scores moderately positively correlated with left parietal rCBF ratio.

Correlations with specific symptoms have been also reported in three cross-sectional studies. Two studies reported negative associations between hallucinations and temporal and occipital rCBF (Mathew et al., 1982; Dousse et al., 1988), perhaps consistent with suggestions that hallucinations are associated with changes in cortical regions underlying the sensory modality of the hallucination (Allen et al., 2008). Temporal rCBF was also positively correlated with suspiciousness, whilst left parietal rCBF correlated with withdrawal and several regions correlated positively with unusual thought content (Mathew et al., 1988).

3.4.2. Longitudinal studies

Unlike cross-sectional designs, longitudinal studies allow changes in symptoms during treatment to be investigated. Five longitudinal studies reported no significant correlations between rCBF at either baseline or follow-up and psychotic symptom scores (Miller et al., 1997a, 1997b; Livingston et al., 1998; Novak et al., 2005; Yildiz et al., 2000). One study reported greater frontal rCBF in more 'behaviourally disturbed' patients (Warkentin et al., 1990).

Six longitudinal studies reported clinical improvement following antipsychotic treatment (Warkentin et al., 1990; Sabri et al., 1997; Erkwoh et al., 1997; Livingston et al., 1998; Yildiz et al., 2000; Sharafi, 2005) although four found improvement in positive but not negative symptoms (Sabri et al., 1997; Erkwoh et al., 1997; Livingston et al., 1998; Miller et al., 2001). In two studies rCBF in several regions correlated with positive symptoms before but not after treatment (Sabri et al., 1997; Erkwoh et al., 1997). In these studies, higher severity of delusions, hallucinations and suspiciousness correlated with lower frontal, cingulate, temporal and thalamic rCBF, whilst more severe formal thought disorder and grandiosity were associated with higher frontal and temporal rCBF at baseline. Stereotypy was the only negative symptom associated with rCBF at baseline, with reported positive associations in left frontal, parietal and temporal regions. Following treatment, positive symptoms tended to have remitted, although several regions showed associations with negative symptoms. Also, frontal, temporal, thalamic and BG flow was negatively correlated with flat affect, withdrawal, abstract thinking and stereotypy (Sabri et al., 1997; Erkwoh et al., 1997).

In summary, presence of positive symptoms has been consistently associated with rCBF in several regions and tended to remit following antipsychotic treatment. In contrast, fewer negative symptoms were associated with rCBF at baseline, although several were associated with regional rCBF at follow up. Negative symptoms remain difficult to treat, despite the introduction of SGAs, reported to have greater efficacy in this symptom domain. In addition, there may be aetiological heterogeneity amongst negative symptoms, which may explain inconsistencies in the association with brain physiology measures.

3.5. Perfusion and treatment response

A priori definitions of treatment response may reveal regions important for antipsychotic action and potentially facilitate prediction of response. Four longitudinal studies looked at treatment response in this manner (Rodriguez et al., 1996, 1997; Lahti et al., 2009; Ertugrul et al., 2009).

In two studies of refractory patients switched from FGA to clozapine for six months, good response to clozapine was associated with higher baseline (FGA-treated) BG rCBF, which decreased following switching (Rodriguez et al., 1997). In contrast, non-response to clozapine was associated with lower BG rCBF, which remained unaltered following treatment, suggesting that baseline and change carry some predictive value in response to this antipsychotic. Importantly, patients were receiving antipsychotics at the time of the baseline scan and therefore the possibility that antipsychotic action could already be associated with some elevation in BG rCBF in responders cannot be dismissed. In line with this, a placebo-controlled, blind and randomised trial, demonstrated that increased ventral striatal rCBF was associated with a good response after one week and six weeks treatment with both haloperidol and olanzapine (Lahti et al., 2009). Increased thalamic and lower hippocampal rCBF were also related to good response to haloperidol at six weeks, whilst higher cerebellar rCBF and lower medial frontal, parietal and anterior cingulate cortex rCBF were related to response to olanzapine.

Associations between rCBF in the thalamus and frontal cortex with 'response' or symptoms were also reported. Rodriguez et al. (1997) reported that increased baseline rCBF in the dorsolateral prefrontal cortex (dlPFC) was evident in responders and decreased

Table 4
Methodological quality of studies included in the meta-analysis.

Study	Same CT/MRI scanner and sequence	Antipsychotic naïve patient group	Drugs administered in controlled manner (dose)	Drugs administered in controlled manner (duration)	Withdrawals explained	Global rCBF controlled for in analysis	Total score for quality (max. 6)
Miller et al. (1997a)	1	0.5	0	0.5	1	1	4
Lahti et al. (2003)	1	0	1	0	1	0	3
Lahti et al. (2009)	1	0	1	1	1	0	4

Each criteria was scored as follows: (1) same scanner and sequence used for each subject (different scanner or sequence = 0, same scanner and sequence = 1); (2) patient group was antipsychotic-naïve (yes = 1, mixed group = 0.5, no = 0); (3) drugs administered according to a protocol for dose regime (yes = 1, no = 0); (4) drugs administered according to a protocol for duration (yes = 1, no = 0); (5) withdrawals explained (yes/none reported = 1, no = 0); (6) global rCBF controlled for in analysis (yes = 1, no = 0).

with treatment. Thalamic and prefrontal rCBF ratios (using the homolateral cerebellar hemisphere value as a reference) correctly predicted response in 78.9% of cases. Ertugrul et al. (2009) reported that baseline frontal/thalamus rCBF predicted percentage change in Positive and Negative Syndrome Scale of Schizophrenia (PANSS) score following eight weeks of clozapine. It is noteworthy that the remission criteria used in this study did not relate to clinical remission and therefore 'treatment responders' may have still been severely ill.

Previous exposure to antipsychotics makes it difficult to discern whether these effects resulted from treatment withdrawal, chronic antipsychotic use or the study drug. Further work should elucidate which biomarkers can predict treatment response to translate such findings to clinical settings to aid personalisation of treatment for schizophrenia.

3.6. Meta-analysis

3.6.1. Study quality

Table 4 shows the results of the quality assessment. Studies scored on average 3.7 out of 6. Most studies did not recruit an antipsychotic-naïve patient group, but this is not unusual, as it can be methodologically difficult to recruit a large enough sample of this kind. No study was considered of such poor quality that they should be excluded from the meta-analysis, especially considering the exploratory nature of this analysis. However, caveats stated elsewhere in this paper should be borne in mind when interpreting the results.

3.6.2. Meta-analysis results

Three longitudinal studies were identified for inclusion in a meta-analysis (Miller et al., 1997a; Lahti et al., 2003, 2009). Although the number of studies was small, data of five groups of patients was available and it was judged that supplementing the above qualitative review with quantitative coordinate-based data was of value in determining brain regions with associations with rCBF and antipsychotic use. However, results should be interpreted with caution, due to the small number of datasets and the exploratory nature of the analysis.

Five groups of patients were available for analysis, as one study presented data for one group of patients (Miller et al., 1997a) and two studies presented data for two groups of patients each treated with different antipsychotics (Lahti et al., 2003, 2009). The data were resampled in this manner to allow extraction of peak coordinates from the papers, which were presented separately for each antipsychotic administered. Coordinates for these groups of patients as a whole were not available.

Lahti et al. (2003) recruited six patients, four of which were scanned at baseline, then following haloperidol and again after treatment with clozapine, thus giving data for two overlapping groups of five patients. Lahti et al. (2009) treated patients with either haloperidol or olanzapine in two independent samples. This gave five patients groups (Table 5), two (non-independent) groups from Lahti et al. (2003), two independent groups from Lahti et al. (2009) and a single group from Miller et al. (1997a). The final sample included 56 patients scanned before and after treatment.

Results (Table 5) revealed a large cluster in the left caudate representing increased rCBF following treatment with antipsychotic medication ($Z = 2.981$; $p < 0.0001$). Decreases in rCBF after treatment were evident in the right medial frontal gyrus ($Z = -3.597$; $p < 0.0001$), cerebellum (right uvula; $Z = -3.539$; $p < 0.0001$ and left declive; $Z = -2.231$; $p < 0.001$) and right thalamus ($Z = -2.052$; $p < 0.01$). These regional alterations are shown in Fig. 1 overlaid on a template (Table 6).

3.6.3. Robustness of the results

Robustness of the results was tested via two supplementary analyses: heterogeneity analysis and jack-knife analysis. The jack-knife analysis is a type of sensitivity analysis which supplements the main meta-analytical findings and indicates how robust they are with respect to study inclusion. Jack-knife resampling determines how sensitive the final results are to leaving different studies out of the analysis. The number of jack-knife resampling analyses is equal to the number of datasets included, and in each analysis a dataset is excluded in turn.

Additionally, the analysis was separately rerun excluding both patient groups from Lahti et al. (2003) and then again excluding both patient groups from Lahti et al. (2009) to ensure that the methodology of particular studies did not drive the results.

Heterogeneity analysis reveals regions showing between-study variability. This analysis showed two of the regions identified had high heterogeneity: the right medial frontal gyrus and the right uvula. This suggests that reductions in these regions are perhaps less robust.

In the jack-knife analysis the left caudate remained significant in three out of five analyses. The most replicable decrease in rCBF was in the right medial frontal gyrus, which only failed to remain significant in one combination out of five. Decreases in rCBF in the right thalamus also remained significant in three out of five combinations. Other significant clusters from the main analysis failed to remain significant in more than two combinations. Rerunning the analysis excluding all patients from Lahti et al. (2003), showed all changes remained significant except the left declive decrease. When excluding all patients from Lahti et al. (2009), only the right medial frontal gyrus cluster remained significant, suggesting the other findings may be driven by this study. Thus overall the decrease in the right medial frontal gyrus was the most robust finding followed by increases in the right thalamus. However the cerebellar findings were less reliable.

These analyses support some of the findings seen in the systematic review and suggest antipsychotics are robustly associated with increased rCBF in the caudate and decreased rCBF in frontal cortical regions.

Table 5
Subset of studies included in an exploratory meta-analysis, with reported regions and co-ordinates.

Study	Patients (*n*)	Antipsychotic prescribed	Coordinates and region identified with increased CBF		Coordinates and region identified with decreased CBF	
Lahti et al. (2003)	5	Haloperidol	28, 8, −12	Right ventral striatum	28, −40, −6	Right hippocampus
			−20, 16, 6	Left caudate	−46, 12, −2	Left insula/ventrolateral frontal
			−30, −4, 6	Left putamen	52, 16, 16	Right dorsolateral frontal
			46, 32, 42	Right dorsolateral frontal	8, −80, −16	Right occipital
					−18, −98, −14	Left occipital
Lahti et al. (2003)	5	Clozapine	32, 4, −12	Right ventral striatum	−30, −28, −10	Left hippocampus
			−14, 8, 16	Left caudate	50, 34, −4	Right ventrolateral frontal
			34, 22, 22	Right dorsolateral frontal	−44, 34, −6	Left ventrolateral frontal
			−50, −8, 26	Left dorsolateral frontal	10, 64, 2	Superior frontal
			−26, 16, 36	Left dorsolateral frontal	−38, 2, 52	Left sensory motor
Lahti et al. (2009)	12	Haloperidol	−22, 12, 6	Left putamen/ventral striatum	34, −78, −26	Right cerebellum
			−20, 4, −10		48, −48, −38	
			34, −40, 44	Right inferior parietal	22, −76, −28	
			34, −34, 50		50, 6, −2	Right insula/superior temporal/inferior frontal
			28, 8, 6	Right putamen	40, 14, −14	
			18, 16, −6	Ventral striatum	−46, −66, −46	Left cerebellum
			28, 0, −10		−14, −74, −32	
			−44, −14, 30	Left post central cortex	−14, −84, −28	
			−38, −18, 18		−46, 6, −8	Left superior temporal
			−16, −14, 0	Left thalamus	28, 38, 38	Right superior frontal
			−6, 6, −4	Left caudate	60, −22, −28	Right inferior temporal
			−8, 2, 4		10, 58, 18	Anterior cingulate cortex/medial frontal cortex
			−18, −24, 58	Left post central cortex	4, 60, 0	
			−48, −44, 32	Left inferior parietal	−34, 12, 10	Left insula/superior temporal/inferior frontal
			−42, −40, 44		54, −60, 38	Right inferior parietal/gyrus angularis
					58, −60, 38	
					64, −50, −6	Right middle temporal
					62, −42, −14	
					58, −2, −30	Right middle temporal
					24, −24, −12	Right parahippocampus
					−8, −14, −18	Midbrain
Lahti et al. (2009)	17	Olanzapine	66, −14, 16	Right post central cortex	0, 52, 22	Anterior cingulate cortex/medial frontal
			58, −46, 38	Right inferior parietal	14, −18, 12	Right thalamus
			60, −30, 36		20, −20, 2	
			16, −56, 66	Right superior	10, −78, −22	Cerebellum
			30, −62, 60	parietal/superior	14, −92, −14	
			24, −72, 46	occipital	12, −66, −18	
			50, −36, −2	Right middle temporal	−10, −12, −14	Midbrain
			58, −32, −12		−12, −26, 2	Left thalamus
			−28, −54, 64	Left superior parietal		
			−22, −60, 60			
			−42, 22, 28	Left middle/inferior frontal		
			8, 4, −10	Right ventral striatum		
Miller et al. (1997a, 1997b)	17	Various (65% first generation, 35% second generation)	−13, 5, −6	Left putamen	−27, 18, 38	Left dorsolateral frontal
			−28, −83, −2	Left fusiform	10, 36, −28	Inferior frontal
					3, 43, 16	Anterior cingulate cortex
					−24, −84, −26	Left cerebellum
					26, −80, −24	Right cerebellum

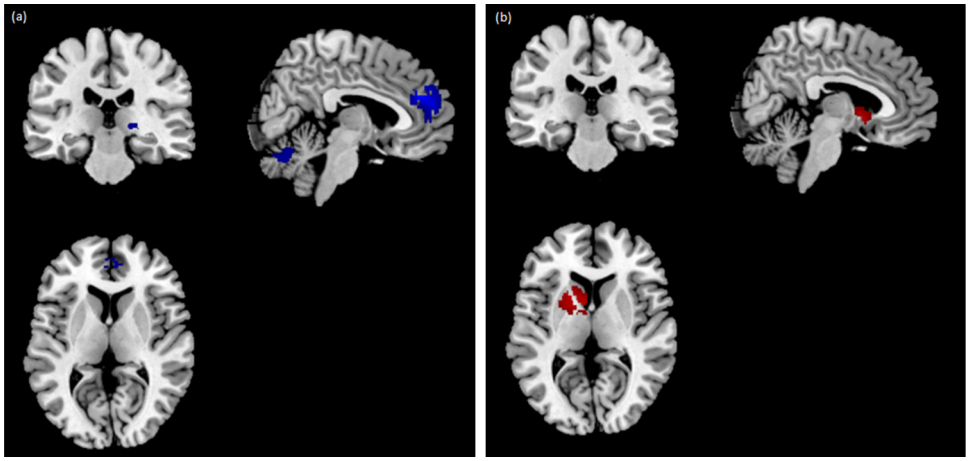


Fig. 1. Main (a) increased (red) rCBF in left caudate and (b) decreased (blue) rCBF in medial frontal gyrus, cerebellum and right thalamus, following antipsychotic treatment in patients with schizophrenia. Significant regions are overlaid on a template from MRIcron (www.mricro.com/mricron) for illustration.

Table 6
Regions identified by the SDM analysis as showing significant increases or decreases in rCBF following antipsychotic treatment.

Brain region	Talairach coordinates	*Z* score	*p* value
Increased rCBF			
Left caudate	−6, 8, −2	2.981	$p < 0.0001$
Decreased rCBF			
Right medial frontal gyrus	6, 42, 24	−3.597	$p < 0.0001$
Cerebellum (right uvula)	16, −76, −24	−3.539	$p < 0.0001$
Cerebellum (left declive)	−16, −86, −22	−2.231	$p < 0.001$
Right thalamus	20, −24, 0	−2.052	$p < 0.01$

4. Conclusions

These studies do suggest that antipsychotic medications induce changes in rCBF, particularly in striatal, frontal and temporal regions, which are also reported to show structural changes (Dazzan et al., 2005; Navari and Dazzan, 2009). This review also provides further evidence that different antipsychotics have different regional effects on rCBF. Although some of these changes appear to be associated with clinical improvement, the ways in which patterns of brain physiology relate to symptoms is still not clear. Altogether, this evidence suggests rCBF is a good candidate biomarker for treatment response to antipsychotics, although very few studies have investigated this potential thus far.

4.1. Differential antipsychotic effects on regional rCBF

Various study designs and methodologies have shown global and regional alterations in rCBF following administration of a number of antipsychotic drugs. Longitudinal studies provide the most consistent evidence that antipsychotics affect rCBF regionally, within hours and even minutes after administration. Longer term changes are also observed in multiple-dose studies, with striatal, frontal and temporal regions most consistently implicated. Still, studies have been small and tended to produce mixed findings. Evidence from cross-sectional studies is less strong, with many studies failing to account for medication status or finding no differences when medicated and unmedicated patients are compared. This may be due to methodological inconsistencies and subject heterogeneity, including differences in previous antipsychotic exposure or the use of multiple antipsychotics.

The mechanisms by which antipsychotic medications lead to alterations in rCBF remain unclear. The concept of neurovascular coupling suggests that rCBF reflects metabolism, such that areas of enhanced post-synaptic activity have a greater metabolic demand, and that perfusion is modulated to meet this demand (Logothetis et al., 2001). Rather than reflecting spiking activity, haemodynamic changes may depend upon synaptic processes, with postsynaptic metabolism making the greatest contribution (Lauritzen, 2001).

All currently licensed antipsychotics antagonise the D2 dopamine receptor and treatment response has been shown to be related to the level of D2 occupancy (Kapur et al., 2000). It would be expected therefore that changes occur in areas more densely populated with D2 receptors, such as the striatum. Antagonism at these receptors would lead to alterations in neurotransmitter turnover, in turn inducing metabolic and perfusion changes. It is possible that increased rCBF reflects increased presynaptic synthesis and release of dopamine due to decreased negative feedback via autoreceptors. Meanwhile, decreased rCBF in frontal and temporal regions may reflect either inhibitory or excitatory downstream effects, in areas that are innervated by densely D2 populated regions.

Furthermore, antipsychotics from different generations may induce different effects on rCBF, with indications that atypicality may be responsible for some of these differences. Our results support this assertion, as greater subcortical effects (particularly in the BG) are evident following treatment with FGAs and greater cortical effects following treatment with SGAs. These differences may reflect the receptor binding profiles of FGAs and SGAs. Compared to FGA, SGAs tend to bind with less affinity to D2 receptors and show more affinity for the serotoninergic system, particularly 5HT2A receptors. The balance between the effects at each of these receptors decreases the effective occupancy at D2 receptors of a particular dose (Stahl, 2003).

Understanding differences in the mechanisms underlying antipsychotic action of different medications could aid clinical management in schizophrenia. It can illuminate the different clinical characteristics of the drugs, for example changes induced by FGA in the BG may underlie the motor side effects more frequently associated with these drugs. Furthermore, it may facilitate stratified medicine, whereby treatment could be more targeted, taking into account individual neurobiology. Finally, it also highlights the importance of carefully considering dose and duration of treatment and type of antipsychotic used in the design and interpretation of neuroimaging studies.

4.2. Correlations between rCBF and clinical measures

If antipsychotics do have specific, regional effects on rCBF, it can be questioned how these changes relate to clinical variables. The evidence reviewed suggests a relationship between rCBF and either composite symptom scores (such as total BPRS score) or specific symptoms, with positive symptoms particularly related to frontal and temporal perfusion at baseline but few negative symptoms showing correlations with rCBF before treatment.

Furthermore, longitudinal studies suggest that following treatment positive symptoms tend to remit, whilst negative symptoms are seen at follow up and are associated with frontal, temporal, thalamic and BG perfusion. Clinical reports and research both suggest that negative symptoms often fail to remit following antipsychotic treatment. The underlying aetiology and neurobiological dysfunction associated with negative symptoms must be elucidated in order to develop new medications that can effectively treat them. Measures of physiology such as rCBF have the potential to allow stratification of patients according to symptomatology and related perfusion patterns. In addition, understanding the brain physiology underlying psychotic symptoms and alterations with treatment is also a prerequisite for establishing rCBF as a marker of treatment response.

Unfortunately, relating imaging measures to clinical measures in schizophrenia has proven difficult, with small sample sizes, poor measurement reliability and validity, difficulties inferring causation and medication impeding attempts to uncover the primary pathophysiology of symptoms (Mathalon and Ford, 2012). Interpreting localised alterations in perfusion in relation to symptoms should be done with care. Medication may have an effect on the neurovasculature that is widespread across the brain. Yet, even when global changes are accounted for (as, for example, in Handley et al., 2012) regional changes remain, suggesting specific vascular effects occur in areas such as the BG. What exactly these regional changes represent and how best to relate them to psychiatric symptoms is still a matter of contention. One should be wary of interpreting such changes in perfusion as altered patterns of activation, as several factors can influence brain haemodynamics besides neural activity.

4.3. Predicting treatment response

The evidence reviewed suggests that neurophysiological measures such as perfusion of the BG, thalamic and frontal regions may relate to the effect of antipsychotic treatment, and thus prove useful in predicting later response to treatment. However, very few studies investigated the predictive value of rCBF using predetermined definitions of treatment response. Conceptualising good response is important in order to standardise across studies, to provide testable a priori hypotheses and to ensure clinical applicability of remission criteria. Advancing our knowledge on the potential predictive role of rCBF could inform attempts to personalise treatment of schizophrenia and provide novel targets for development of new medications.

4.4. Implications for future research

rCBF may provide a useful predictive biomarker for treatment response to antipsychotics in schizophrenia. While functional magnetic resonance imaging (fMRI) data represent a complicated mix of parameters (rCBF, cerebral blood volume and oxygen consumption), perfusion imaging can provide absolute quantification of a single parameter either at rest or within an activation paradigm.

Resting CBF provides information on basal brain activity and understanding the effects of antipsychotics on this physiological marker may also help clarifying which mechanisms underlie other (structural and functional) illness-related brain changes (Scheepers et al., 2001). Of note, changes in rCBF patterns following antipsychotic administration occur in the same brain regions reported as altered in psychosis. Additionally, CBF is closely correlated with neuronal metabolic measures (Raichle et al., 1976) and modern perfusion techniques such as arterial spin labelling (ASL) provide measures of CBF that correlate with regional brain activity measured using other techniques (Uludag et al., 2004). Furthermore, ASL is non-invasive and since it does not require ionising radiation, is ideally suited to the multiple-point, longitudinal evaluation required in pharmaco-imaging studies. This review suggests that baseline patterns of rCBF and changes with treatment in rCBF are related to treatment response to antipsychotics and there is promise that these differences predict clinical outcomes.

Identifying biomarkers to predict treatment response in schizophrenia is a major goal of translational psychiatry and could inform interventions, allowing the illness course to be altered early on. The hope for the future however is that much subtler differences in brain structure, physiology and chemistry will be identified to aid differential diagnosis and allow individualised prescribing and treatment planning depending on individual biology and clinical presentation of patients.

Appendix A.

A.1. Estimation of effect sizes

For all contrasts and associations, reported estimates of the strength of the effects were extracted when given (either Pearson's *r*, or Cohen's *d*). Where these were not reported but could be calculated from the data in the original paper, a Cohen's *d* effect size estimate was calculated using the formulae below (Thalheimer and Cook, 2002). Otherwise, the statistical test and *p* value are reported as in the original paper.

For independent groups:

$$\frac{\text{Mean rCBF of experimental group} - \text{Mean rCBF of control group}}{\text{Pooled standard deviation}}$$

For dependent groups:

Although effect sizes would be ideally calculated using a mean rCBF change score in patients and controls, together with a pooled standard deviation of the change, rCBF change scores are rarely reported for both patients and controls. In most studies, controls are only scanned on one occasion and so change scores cannot always be calculated. For these studies, the following formula was used to calculate an effect size estimate for the change in patients (Dunlop et al., 1996):

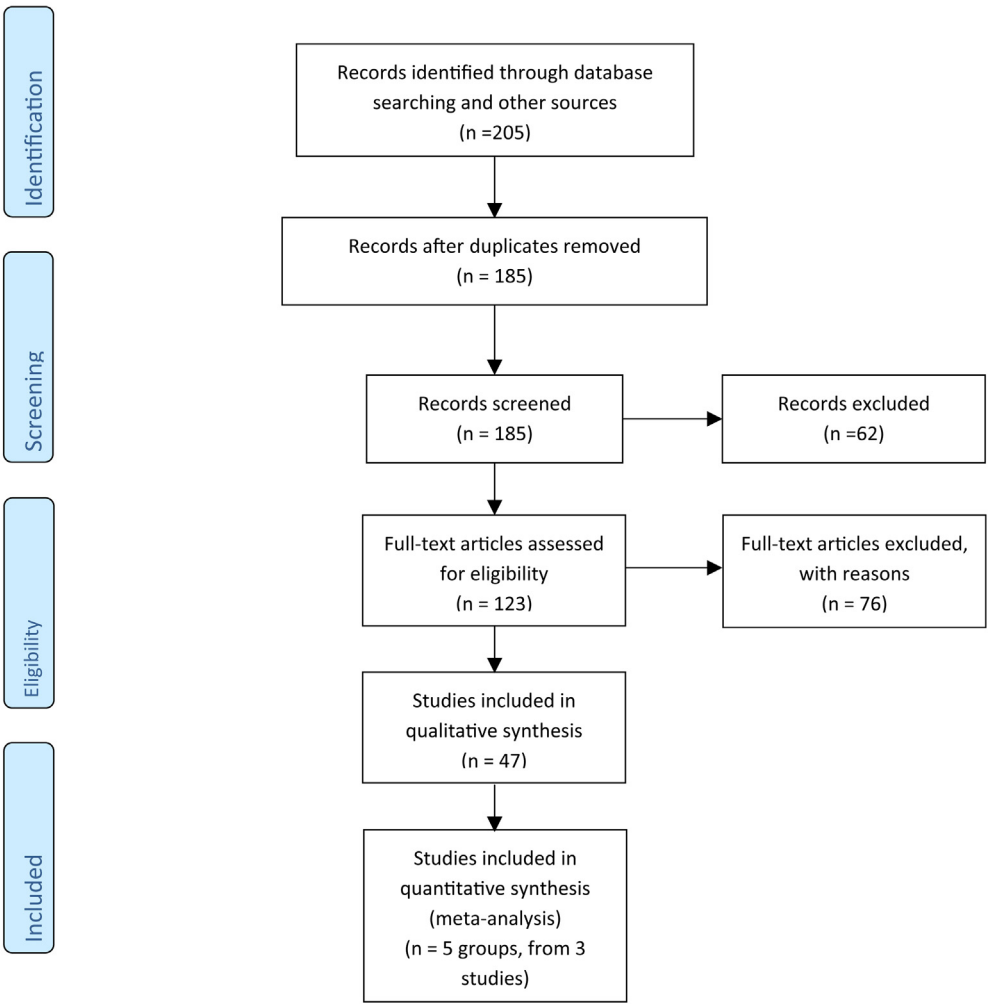
$$\frac{\text{Mean rCBF (baseline)} - \text{Mean rCBF (follow-up)}}{\text{Pooled standard deviation (baseline and follow-up)}}$$

When an effect size could not be calculated from the data available, the statistical test and the *p* value were reported as in the original paper. When papers reported *t*-tests or *F*-tests, we calculated effect sizes (Thalheimer and Cook, 2002).

We grouped studies according to study design: cross-sectional, longitudinal single-dose, and longitudinal multiple-dose. Results of the cross-sectional studies are presented for each comparison (schizophrenia patients versus healthy controls, medicated schizophrenia versus unmedicated schizophrenia). Longitudinal studies contrast pre-treatment and post-treatment rCBF in a single group or compare patients and controls before and after treatment. We also report results for studies comparing treatment with different antipsychotic generation and those reporting associations with clinical variables or treatment response.

Appendix B.

PRISMA Flow Diagram



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